Exploring the boundaries of Bariatric Surgery

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EXPLORING THE BOUNDARIES OF BARIATRIC SURGERY

Should we introduce it to adolescents and can we innovate traditional surgery?

ACADEMISCH PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 16 april 2021 om 14.00 uur

door

Givan Florian Paulus

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General Introduction

OBESITY IN CHILDREN AND ADULTS

Obesity is rapidly becoming an extreme global epidemic in adults, adolescents and even children (1). This is a major concern since excess weight leads to impaired health. Overweight in adults is defined as a body mass index (BMI, weight/height²) >25 kg/m², obesity as a BMI >30 kg/m² and extreme obesity as a BMI >35 kg/m². When extreme obesity is accompanied by obesity-related health conditions or BMI exceeds 40 kg/m², it is known as morbid obesity. The 'normal' proportions of the body change with age. Therefore, there are age-adjusted cut-offs for children and adolescents (2).

Since 1975, the prevalence of obesity in the world has almost tripled. More than 650 million people are currently obese, corresponding to 13% of the adult population. An impressing 40 million of them are adolescents (2). In the US 13% of the adolescents are extremely obese (3). In the Netherlands nearly half of all adults are overweight, while 14.2% are obese. In Dutch children and adolescents, the prevalence of obesity was 2.7% in 2018 (4).

IMPACT OF OBESITY

Overweight and obesity are associated with serious comorbidity such as type 2 diabetes mellitus (T2DM), hypertension (HT), obstructive sleep apnea syndrome (OSAS), dyslipidemia, non-alcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS), asthma, musculoskeletal disorders and gastroesophageal reflux disease (GERD) (5–7). The risk of dying from any obesity related cause increases by 6-7% for every 2 years lived with obesity (8). Furthermore, obesity reduces quality of life. Obese adolescents are likely to suffer from psychological morbidity, which has the potential to scar them for life (9). For example, Viner and Cole showed in a birth cohort from 1970 that persistent obesity in women was associated with higher risk of never being gainfully employed and not having a current partner (10). These findings urge us to find ways to treat obesity effectively and early in life. To emphasize the importance of treating obesity, the American Medical Association has decided to officially recognize obesity as a chronic disease in 2013. Fortunately, the negative health effects of obesity are, at least partially, reversible. Treatment of obesity has shown to reduce comorbidity and improve quality of life. Furthermore, greater weight loss results in greater improvement (11, 12).

DEVELOPMENT OF OBESITY IS MULTIFACTORIAL

Overweight and obesity develop when energy intake exceeds energy expenditure. The excess energy is stored in fat cells, which accumulate in the body and a person becomes overweight. However, there are many factors that contribute to this impaired balance.

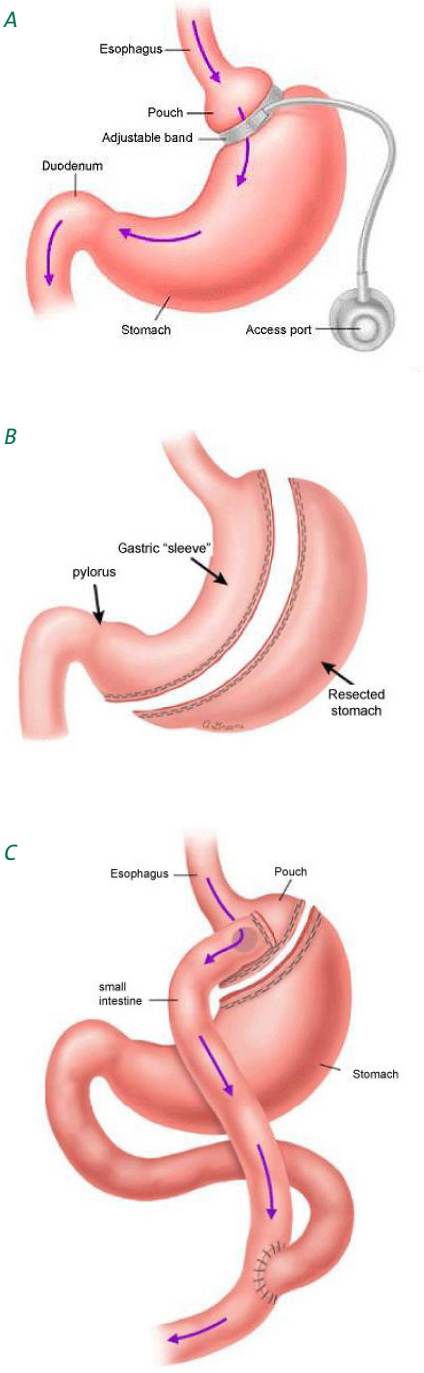
Our environment is progressively becoming obesogenic. During evolution, the human body has developed to protect itself from weight loss in times of absence of food, but it has only weak defenses against weight gain when food is abundant. Energy dense food is widely available and often cheaper than healthy food, while physical activity has decreased because of physically non-demanding jobs, changed forms of transportation and increasing urbanization in a civilization in which exercise plays no regular part in people's lives (2, 13, 14).

The physiological balance between food intake and energy expenditure is called energy homeostasis. Feelings of hunger and satiety are stimulated or inhibited by endocrine systems that influence this balance. The fasted plasma levels and food induced plasma changes of the gut derived peptides ghrelin ('the hunger hormone'), GLP-1 and PYY (satiety hormones) are known to be different in obese subjects and to change after weight loss (15–18).

However, there is also a drive to eat to obtain pleasure in the absence of an energy deficit, associated to food-reward, called hedonic hunger. Studies have shown that obese subjects have a greater motivation to obtain and consume food without physical demand, especially during stress (19–21). This can be quantified with 'wanting and liking' computer tasks and questionnaires assessing behavior towards food.

BARIATRIC SURGERY

Overweight and obesity should initially be treated with a combined lifestyle intervention focusing on behavioral and dietary modifications. However, in morbidly obese adults, only bariatric surgery has proven to be effective in the long term (2, 22, 23). In obese children, combined lifestyle intervention is often effective in short term, while long term effects are relatively disappointing. A Cochrane review shows a maximum of 1.7 kg/m² BMI loss after 12 months of lifestyle intervention (24). International guidelines for the treatment of obesity advise operative treatment for subjects with morbid obesity (22). In weight loss surgery – or bariatric surgery – the anatomy of the gastrointestinal tract is altered. The procedures were initially developed to cause physical restriction of the amount of intake and/or to induce malabsorption by altering the pathway through the digestive tract. However, it is now clear that bariatric procedures result in weight loss and metabolic improvement by other mechanisms than restric-



tion or malabsorption alone. Reduced energy intake, as a result of altered eating behavior, is the main driver for weight loss in humans following bariatric surgery. The biological mediators underlying altered eating behavior are not yet fully understood, but altered responses of gut hormones, bile acid and the microbiome are key candidates (25, 26).

Gastric banding is an example of a restrictive technique (Figure 1.1-A). The gastric capacity is decreased by creating a small pouch with an adjustable silicon band around the upper part of the stomach. The band can then be inflated or deflated through a subcutaneous port to achieve the optimal food restriction. Another restrictive technique is the sleeve gastrectomy, in which a large portion of the stomach is surgically removed by stapling along the greater curvature (Figure 1.1-B). This also causes ghrelin levels to drop, because most ghrelin producing cells are found in the stomach, which is assumed to have beneficial effects on feelings of hunger. A procedure that was developed to combine restriction and malabsorption is the Roux-en-Y gastric bypass (Figure 1.1-C). A small gastric pouch is created through transection of the stomach. This pouch is connected to the middle portion

Figure 1.1 | *Traditional surgical techniques. Adapted from Nielsen et al (37).*

A) Adjustable gastric banding

B) Sleeve gastrectomy

C) Roux-en-Y gastric bypass

of the small intestine, bypassing the remaining stomach and the proximal small intestine (27, 28). Excess weight loss after both gastric bypass and sleeve gastrectomy is approximately 65% to 70% and approximately 45% to 50% after adjustable gastric banding (29). However, these procedures are associated with considerable morbidity (30–35). The most common adverse events after laparoscopic Roux-en-Y gastric bypass include wound infection (3.0%), anastomotic leakage (2.1%), and, in the longer term, anastomotic stenosis (4.7%) and internal herniation (1.1%) (35, 36). The mortality rate of gastric bypass surgery varies between 0.2% (laparoscopic) and 0.9% (open) (35, 36). The sleeve gastrectomy is an increasingly popular technique, but it also has a significant leak risk of 2.4% (33).

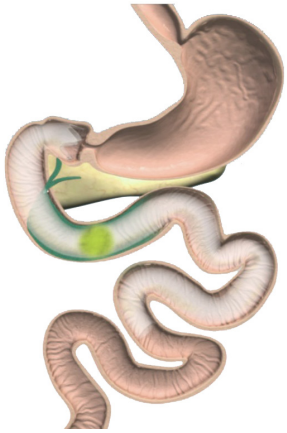
In the last decades, bariatric procedures have also been studied in obese adolescents. Potential adverse effects on growth and development in prepubertal patients who have not reached full maturity raise concerns. However, bariatric surgery relatively early in life intervenes before comorbidities become irreversible and reduces the risk of surgical complications. The last few years, indication criteria for bariatric surgery have expanded, and surgical techniques have improved. However, the outcome and best techniques to treat morbidly obese adolescents remain relatively unknown.

INNOVATIVE BARIATRIC APPROACHES

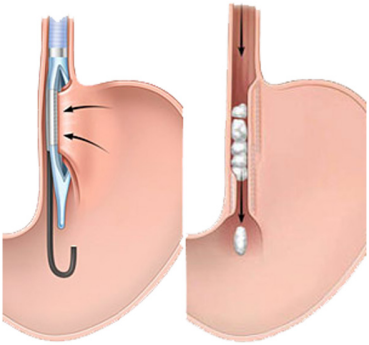
Bariatric surgery is indicated when the expected health gain exceeds the risk of surgery. This implicates that fragile patients with a high risk of adverse events and patients who do not meet the current criteria for bariatric surgery (i.e., patients who are "not heavy enough") cannot profit from its advantages. Minimally invasive procedures that are able to cause weight loss through food restriction, malabsorption and/or changed eating behavior may provide an attractive and possibly less-expensive alternative for potential beneficiaries. Examples of gastroscopic procedures such as the EndoBarrier (Figure 1.2-A), Transoral Endoscopic Vertical Gastroplasty (TOGA , Figure 1.2-B) and Primary Obesity Surgery Endoluminal (POSE, Figure 1.2-C) procedure have been published in other studies (38-41). The first procedure targets malabsorption and altered GI physiology, whereas the latter procedures are restrictive. In this thesis we present a new trans oral restrictive procedure with the articulating circular endoscopic (ACE) stapler.

A different approach to minimal invasive bariatric surgery is with implantable gastric electrical stimulation (GES, Figure 1.2-D) (42, 43). Weight loss is achieved by impairing gastric motor function and by modulating signaling from the stomach to the brain (44). Initial results with the Transcend implantable gastric stimulator were promising,

Figure 1.2 | *Innovative surgical techniques*



A) EndoBarrier

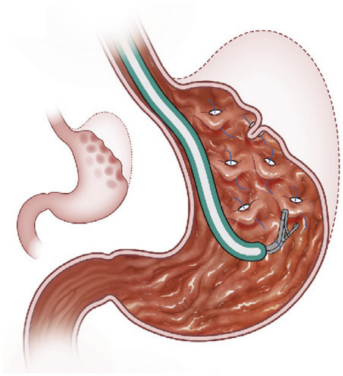


B) Transoral Endoscopic Vertical Gastroplasty

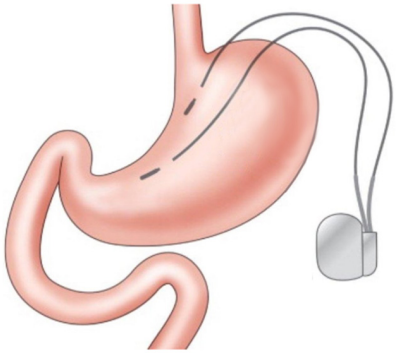
but consecutive double-blind randomized controlled trials initiated between 2000 and 2005, have failed to show a clear effect on body weight relative to sham-stimulated controls (45–47). In a five-year period of extensive animal studies each major component of GES was systematically reexamined. Specific pulse configuration and pre-pyloric pulse delivery led to an optimal delay in gastric emptying and reduction in food intake (48). Moreover, chronic daily delivery of the GES treatment resulted in weight loss. The encouraging results of these animal studies have been used to define the required capabilities of the current Exilis™ system.

AIMS AND OUTLINE OF THIS THESIS

The projects that led to this thesis have in common that they explore the boundaries of bariatric surgery. The BASIC trial was initiated to investigate the pros and cons of laparoscopic adjustable gastric banding in morbidly obese adolescents. Chapter 2 is a review and meta-analysis of the currently available literature. Chapter 3 is a retrospective analysis of a series of morbidly obese adolescents that had bariatric surgery and chapter 4 describes the protocol of the randomized controlled BASIC trial that was initiated and for which data is currently being collected. Chapters 5 to 8 evaluate a completely new bariatric technique. First the safety and preliminary effective-



C) Primary Obesity Surgery Endoluminal



D) Implantable gastric electrical stimulation.

ness of the minimal invasive ACE stapler treatment is studied, after which the impact on health, physiological systems, psychosocial factors and behavior towards food are presented in chapter 6, 7 and 8.

In chapter 9 another first in human study is presented regarding the preliminary effectiveness of the Exilis™ gastric pacer with its impacts on physiological systems and psychosocial changes. The main findings of these studies and their implications for the future are discussed in the 10th and last chapter of this thesis, the general discussion.

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2

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Obesity Surgery. 2015

Bariatric Surgery in Morbidly Obese Adolescents:

A Systematic Review and Meta-Analysis

ABSTRACT

Pubmed, Embase and Cochrane were systematically reviewed for available evidence on bariatric surgery in adolescents. Thirty-seven included studies evaluated the effect of laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (LSG) in patients ≤ 18 years old. Fifteen of 37 studies were prospective; including one RCT. Mean BMI loss after LAGB was 11.6 kg/m² (95% CI 9.8–13.4), versus 16.6 kg/m² (95% CI 13.4–19.8) after RYGB and 14.1 kg/m² (95% CI 10.8–17.5) after LSG. Two unrelated deaths were reported after 495 RYGB procedures.

All three bariatric procedures result in substantial weight loss and improvement of comorbidity with an acceptable complication rate, indicating that surgical intervention is applicable in appropriately selected morbidly obese adolescents.

INTRODUCTION

Obesity is an emerging pandemic phenomenon (1)**.** Over the past three decades, the prevalence of adult obesity in the United States has doubled while that of adolescent obesity has tripled (2). Current estimates classify 33.6% of adolescents living in the US as overweight, 18.4% as obese and 13.0% as being extremely obese, defined as body mass index (BMI) ≥85th, 95th and 97th percentile respectively (3). Individual, social, environmental and economic factors contribute to the development and persistence of morbid obesity.

Adolescent obesity is associated with preventable chronic health conditions like type two diabetes mellitus (T2DM), hypertension, obstructive sleep apnea syndrome (OSAS), dyslipidemia, nonalcoholic steatohepatitis, polycystic ovary syndrome and various musculoskeletal diseases (4, 5). Obese adolescents are likely to suffer from psychological morbidity, loss of self-esteem and social exclusion which has the potential to scar them for life (6). The risk of dying from any obesity related cause increases by 6–7% for every two years lived with obesity (7). These findings urge us to find ways to treat obesity early in life.

Presently, adolescent obesity is mostly managed by combined lifestyle interventions focusing on behavioral and dietary modifications. These treatments are typically initiated and evaluated by a multidisciplinary team including a pediatrician, dietician, psychologist and a physiotherapist. While often effective in short term, long-term effects are relatively disappointing. A recent Cochrane review shows a maximum of 1.7 kg/m² BMI loss after 12 months of lifestyle intervention (8).

In adults, bariatric surgery is extremely effective compared to conservative treatment, resulting in adequate long-term weight loss and reduction of mortality (9). The last decades, various bariatric procedures have been performed in adolescents, including laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty, biliopancreatic diversion and more recently laparoscopic sleeve gastrectomy (LSG). Potential adverse effects on growth and development in pre-pubertal patients who have not reached full maturity raise concerns. However, bariatric surgery relatively early in life intervenes before comorbidities become irreversible and reduces the risk of surgical complications.

Currently, the guidelines from the International Pediatric Endosurgery Group (IPEG) state that adolescents with a BMI > 40 kg/m² or a BMI > 35 kg/m² combined with severe comorbidities should be considered for surgical intervention, if they have (nearly) attained adult stature (10). These guidelines are largely based upon a systematic review and meta-analysis by Treadwell et al. (11), reviewing studies up to December

2007. The last few years, indication criteria for bariatric surgery have expanded and surgical techniques have improved. However, the outcome and best techniques to treat morbidly obese adolescents remain relatively unknown.In this review we evaluate and compare the efficacy, safety and (psychosocial) health benefits of various bariatric surgical techniques as a treatment for morbid obesity in adolescents. Our data are obtained with help of supplemental data from several authors and strengthened by inclusion of the most recent high quality studies.

METHODS

Protocol and registration

This review was conducted according to the PRISMA (12) and MOOSE (13) statements.

Eligibility criteria

Prospective clinical trials and observational studies on LAGB, RYGB and LSG were included with the following inclusion criteria: ≥ 10 patients, mean follow-up ≥ 12 months, age ≤ 18 years at time of operation (and less than 20% > 18 years), majority of procedures < 25 years ago and English full-text available. Meta-analysis of BMI loss was done when BMI loss was either reported or could be calculated.

Search

Pubmed, Embase and Cochrane databases were searched on the 20th of January 2014 with relevant search terms and Medical Subject Headings (MeSH) on LAGB, RYGB and LSG in children and adolescents. Full electronic Pubmed search is presented in Figure 2.1.

Study selection

After electronically removing duplicates using EndNote X6.0.1 (Thomson Reuters), all remaining duplicate entries and aberrant records were manually removed. Two independent researchers (GP and LdV) screened the remaining abstracts and/or full text version and collected the eligible citations. Clinical data and study properties were added to the citations by reviewing all full text articles. Reviewing inclusion period, surgical center, authors and population characteristics identified publications with data overlap, in which case articles presenting the most complete and/or recent data were included.

Pubmed search

```
(
 ("bariatric surgery"[MeSH Terms] OR "bariatric surgery"[All Fields]) OR
"LAGB" [All Fields] OR
"gastric bypass"[All Fields] OR
(("stomach"[MeSH Terms] OR "stomach"[All Fields] OR "gastric"[All Fields]) AND
( "band"[All Fields] OR  sleeve[All Fields])) OR
"banded gastroplasty"[All Fields] OR
("sleeve" [All Fields] AND ("gastrectomy"[MeSH Terms] OR "gastrectomy"[All Fields])) OR
("anastomosis, roux-en-y"[MeSH Terms] OR ("anastomosis"[All Fields] AND "roux-en-y"[All Fields]) OR
"roux-en-y anastomosis"[All Fields] OR "roux en y"[All Fields])
)

AND

("infant"[All Fields] OR "child"[All Fields] OR "adolescent"[All Fields] OR "pediatric"[All Fields])

NOT

("lipectomy"[MeSH Terms] OR "Esophageal and Gastric Varices"[Mesh)
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Figure 2.1 | *Full Pubmed search*

Data collection process

Data relevant for our systematic review and meta-analysis were collected in a data-sheet and completed with data from referenced articles, previous publications or by contacting the corresponding author.

Data items

BMI before and after the procedure or BMI loss with reported variance, complications and change in comorbidity were extracted from each article. When individual patient data were available, mean BMI and variance was calculated for those patients younger than 19 years. Mean BMI at follow-up was only used to calculate BMI loss if more than 50% of the baseline population had reached that moment.

Risk of bias in individual studies

Study characteristics that influence risk of bias (e.g. prospective/retrospective) were assessed and collected in a table. Additionally, two independent reviewers carefully assessed details on the in- and exclusion process, pre-operative lifestyle treatment, post-operative lifestyle support and loss to follow-up.

Summary measures

Mean BMI loss was used for meta-analysis. Corresponding authors were contacted if variance of BMI loss was not reported. Complications and comorbidity resolution were summarized if follow-up was at least 6 months. Minor complications, reported in less than 3 studies, were omitted from the results.

Synthesis of results

Summary effect measure of BMI loss and forest plots were produced with 95% CI for each surgical method using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX). Differences between operative techniques were tested in a random effect model. For missing variances, the square root of the average sample-size-weighted variance from all available variances was used. Data on complications or comorbidities were summarized when they were specifically mentioned. Results from large multicenter database studies were not summarized, while for short-term studies (< 6 months follow-up) only perioperative results were summarized.

Risk of bias across studies

A funnel plot for standard error of BMI loss against BMI loss was used to assess publication bias for each technique. The straight lines indicate the region within which 95% of points should lie in the absence of both heterogeneity and publication bias (Figure 2.4).

Additional analyses

A meta-regression analysis was performed to assess if BMI loss was affected by follow-up duration after the first 12 months, or by different surgical gastric banding techniques (perigastric vs. pars flaccida). Authors were contacted when technical details were not provided. Additionally, differences in baseline BMI of different surgical procedures were tested in a random effect model.

RESULTS

Study selection

The search in Pubmed, Embase and Cochrane provided a total of 4575 citations. After removing duplicates and screening abstracts, 4468 records were excluded and 107 remained for full-text analysis. Seventy full-text articles did not meet the inclusion criteria. Therefore, a total of 37 articles were included, including one article reporting on both LAGB and LSG. Eleven of eighteen LAGB studies, six of thirteen RYGB studies and five of seven LSG studies were eligible for meta-analysis of BMI loss (Table 2.1, Figure 2.2). No additional studies were identified through cross-referencing.

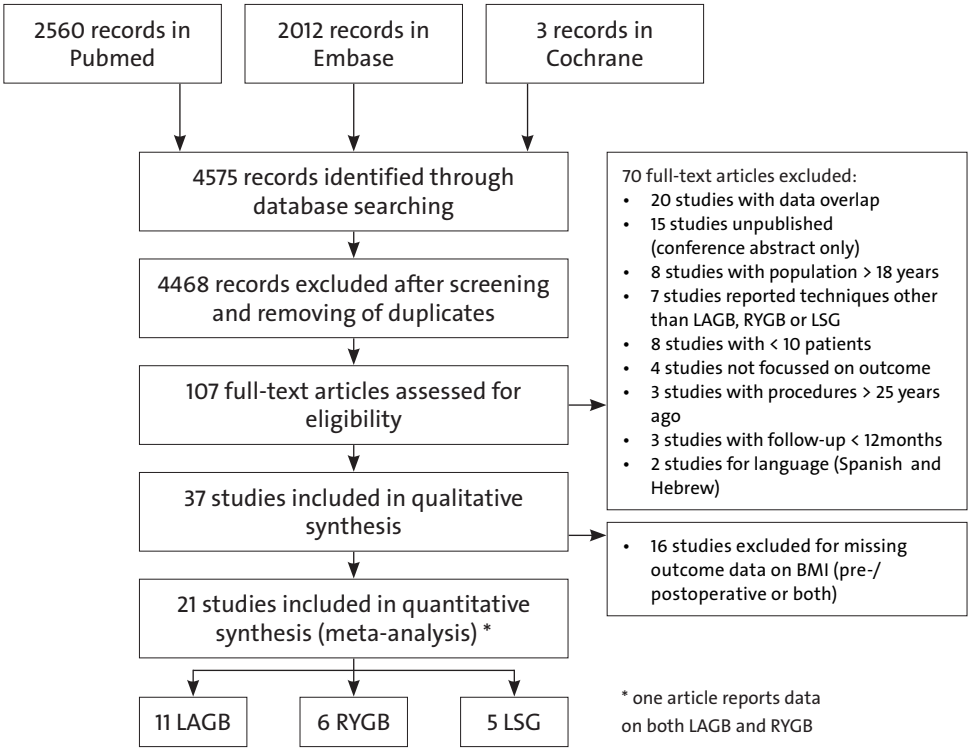


Figure 2.2 | *Paper retrieval schematic*

Table 2.1 | *Study characteristics*

Authors	Operation period	Location	N
Studies on LAGB			
Abu-Abeid et al, 2003 (27)	NR	Tel-Aviv, Israel	11
Al-Qahtani, 2007 (28)	1/2003 – 12/2005	Riyadh, Saudi Arabia	51
Alqahtani, 2011 (29)	6/2004 – 12/2007	Riyadh, Saudi Arabia	50
Angrisani et al, 2005 (30)	1/1996 – 12/2003	Naples, Italy	58
Dolan et al, 2003 (31)	1996 – NR	Brisbane, Australia, Royal Brisbane Hospital	17
Fielding et al, 2005 (32)	1998 – 2003	Brisbane, Australia – Wesley Hospital	41
Holterman et al, 2010 (14)	3/2005 – 6/2007	Chicago, Illinois	20
Inge et al, 2014 (33)	2/2007 – 12/2011	5 centers, US	14
Lee et al, 2012 (34)	2002 – 2011	New York, St.Luke's-Roosevelt Hospital Center	23
Lennerz et al, 2013 (35)	1/2005 – 12/2010	23 centers, Germany	10
Messiah et al, 2013 (36)	4/2004 – 10/2010	360 facilities, US	436
Nadler et al, 2008 (37)	9/2001 – 1/2007	New York, NY, University School of Medicine	73
O'Brien et al, 2010 (15)	5/2005 – 9/2008	Melbourne, Australia	25
Silberhumer et al, 2011 (17)	1998 – 2004	Salzburg/Vienna, Austria	50
Silva et al, 2012 (38)	7/2001 – 6/2010	Oporto, Portugal	14
Varela et al, 2007 (39)	2002 – 2006	59 university centers, US	90
Yitzhak et al, 2006 (18)	2000 – 2003	Beer Sheva, Israel	60
Zitsman et al, 2011 (40)	8/2006 – NR	New York, Columbia University Medical Center	100
Studies on RYGB			
De la Cruz – Munoz et al, 2012 (41)	2001 – 2010	Miami, FL	71
Inge et al, 2004 (42)	2001 – 200 3	Cincinnati, OH	10
Inge et al, 2014 (33)	2/2007 – 12/2011	5 centers, US	161
Lee et al, 2012 (34)	2002 – 2011	New York, NY – St. Luke's-Roosevelt Hospital Center	32
Messiah et al, 2013 (36)	4/2004 – 10/2010	360 facilities, US	454
Miyano et al, 2013 (43)	8/2002 – 5/2007	Cincinnati, OH	77
Nijhawan et al, 2012 (44)	2001 – 2007 (approx.)	San Diego, CA	20
Olbers et al, 2012 (22)	2/2006 – 6/2009	Gothenburg, Sweden	81
Strauss et al, 2001 (45)	4/1985 – 5/1999	New Brunswick, NJ	10
Sugerman et al, 2003 (19)	1981 – 1/2002	Richmond, VA	33
Varela et al, 2007 (39)	2002 – 2006	59 university centers, US	191

Follow-up (months)	Age (years; mean/ range)	Operative technique details	Design	Included for
6 – 36	15.7	Perigastric	Retrospective	M – CO – CM
3 – 34	16.8	Pars flaccida	Retrospective	CM
NR – 60	17	Pars flaccida	Retrospective	CO
0 – 84	18	55 perigastric; 3 pars flaccida	Retrospective	M – CO – CM
12 – 46	16.7	Since 1999 pars flaccida	Prospective	M
1 – 70	15.6	Since 1999 pars flaccida	Retrospective	CO – CM
15 – 42	16	Perigastric	Prospective	M – CO – CM – QOL
1	17.1	Pars flaccida	Prospective	CO
1 – 24	17.2	Pars flaccida	Retrospective	CO – CM
0 – >30	16.7	NA	Prospective	M
0 – 12	18.5	NA	Prospective database	CM
12 – 24	15.8	Pars flaccida	Prospective	M – CO – CM
24	16.5	Pars flaccida	RCT	M – CO – QOL
63 – 138	17.1	Pars flaccida	Retrospective multicenter	M – CO – CM – QOL
12 – 36	16.3	Pars flaccida	Retrospective	M – CO – CM
1	12-18	NA	Retrospective	CO
25 – 65	16	2 pars flaccida techniques	Retrospective	M – CO – CM – QOL
12	14-19	Pars flaccida	NR	M – CO – CM
9 – 15	18.3	NR	Retrospective	M – CO
1– 24	NR	2 open / 8 laparoscopic, handsewn gastro-jejunostomy	Retrospective	CO – CM
1	17.1	NA	Prospective	CO
1 – 24	18.6	Pouch 50 mL/40-cm biliopancreatic limb, 100 cm alimentary limb	Retrospective	CO – CM
12	18.5	NA	Prospective database	CM
3	16.8	Biliopancreatic limb 75-150 cm / 15-30 cm from Treitz / 30-45 mL pouch	Retrospective	CO – CM
60 – 120	16.9	Pouch 15 mL / Roux limb 75 cm	Retrospective	M – CO – CM
24	16.5	Pouch <20 mL / Roux limb 80cm	Prospective	M – CO – CM – QOL
8 – 156	16.2	Pouch 20±5 mL / Roux limb 50 – 150 cm or to distal jejunum	Retrospective	M – CO – CM
1 – 14	16	Standard, long-limb and distal gastric bypass	Retrospective	M – CO – CM
1	12-18	NA	Retrospective	CO

Table 2.1 | *continued*

Authors	Operation period	Location	N
Zeller et al, 2009 (20)	5/2004 – 1/2007	Cincinnati, OH	31
Zeller et al, 2011 (21)	5/2004 – 9/2005	Cincinnati, OH	16 / 14
Studies on LSG			
Aldaqal et al, 2013 (23)	11/2009 – 2/2012	Jeddah, Saudi Arabia	32
Alqahtani et al, 2012 (47)	3/2006 – 2/2011	Riyadh, Saudi Arabia	99
Boza et al, 2012 (48)	1/2006 – 10/2009	Santiago, Chile	51
Inge et al, 2014 (33)	2/2007 – 12/2011	5 centers, US	67
Lennerz et al, 2013 (35)	1/2005 – 12/2010	23 centers, Germany	11
Nadler et al, 2012 (49)	1/2010 – 12/2011	Washington, DC	23
Varela et al, 2007 (39)	2002 – 2006	59 university centers, US	28

Studies included for meta-analysis and systematic review, text in grey if only eligible for semi-quantitative analysis; NR=not reported; NA=not applicable; M=meta-analysis; CO=complications; CM=comorbidity; QOL=Quality of life assessment

Follow-up (months)	Age (years; mean/ range)	Operative technique details	Design	Included for
12	16.4	Pouch 20 mL / 5-10 cm from Treitz / Roux limb 100-150 cm (46)	Prospective	QOL
24	16.2	Pouch 20 mL / 5-10 cm from Treitz / Roux limb 100-150 cm (46)	Prospective	M - QOL
12	15.2	50-80 mL lumen	Prospective	M – CO – CM – QOL
6 – 24	14	NR	Retrospective	M – CO – CM
6 – 24	18	60F calibration catheter	Retrospective	M – CO – CM
1	17.1	NA	Prospective	CO
12	15.4	NA	Prospective	M – CM
9 – 15	17.3	40F Bougie	Retrospective	M – CO – CM
1	12-18	NA	Retrospective	CO

Table 2.2 | *Risk of bias: list of factors that introduce a risk of bias*

Study	In- and exclusion criteria
Gastric banding	
Abu-Abeid et al, 2003 (27)	NIH criteria
Al-Qahtani, 2007 (28)	NIH criteria
Alqahtani, 2011 (29)	NIH criteria
Angrisani et al, 2005 (30)	BMI ≥40 or ≥35 kg/m² with comorbidities; psychiatric and genetic disorders excluded
Dolan et al, 2003 (31)	NR (2/17 patients BMI<35)
Fielding et al, 2005 (32)	BMI ≥40 or ≥35 kg/m² with comorbidities
Holterman et al, 2010 (14)	NIH criteria
Inge et al, 2014 (33)	Pratt (50): BMI ≥35 with major comorbidities and BMI ≥40 with other comorbidities; no binge-purge eating disorders
Lee et al, 2012 (34)	NIH criteria, procedure choice on individual basis
Lennerz et al, 2013 (35)	CAADIP 2010 and IFSO guidelines, procedure choice on individual basis
Messiah et al, 2013 (36)	NA (national database)
Nadler et al, 2008 (37)	NIH criteria
O'Brien et al, 2010 (15)	BMI >35 kg/m², identifiable medical complications, physical limitations or psychosocial difficulties
Silberhumer et al, 2011 (17)	>99.5th age- and gender-adjusted growing percentile, adolescents <14 years old at least one comorbidity
Silva et al, 2012 (38)	IPEG guidelines
Varela et al, 2007 (39)	NA (national database)
Yitzhak et al, 2006 (18)	NIH criteria
Zitsman et al, 2011 (40)	Pratt (50): BMI ≥35 with major comor-bidities and BMI ≥40 with other comorbidities; no binge-purge eating disorders
Gastric bypass	
De la Cruz - Munoz et al, 2012 (41)	NIH criteria
Inge et al, 2004 (42)	BMI ≥40 kg/m² with serious obesity-related comorbidities or BMI ≥50 kg/m² with other comorbidities

Intervention before surgery	Support after surgery	Loss to follow-up
≥1 year dietician	Emotional support	NR
Failure to lose weight for ≥6 months with conservative treatment	Flexible follow-up, reinforcement of the importance of diet and exercise	NR
Failure to lose weight for ≥6 months with conservative treatment	Flexible follow-up, reinforcement of the importance of diet and exercise	NR
≥ 1 year of conservative medical treatment	NR	8% – 12% – 24% (12–36–60 months)
NR	NR	0% – 31% (12–24 months)
'Appropriate pediatric care'	Surgeon alone	2%
4-6 months multidisciplinary program	Behavioral, nutritional, and activity monitoring and monthly counseling	20%
NR	NR	NR
Exercise and diet with nutritionist, educational sessions and psychological and nutritional evaluations	NR	70% (24 months)
NR	Multidisciplinary approach including a pediatrician, child psychologist, surgeon and the primary care provider	53% (LAGB+LSG)
NA	NA	12% - 34% - 63% (3–6-12 months)
NR	First postoperative year monthly to monitor weight loss, appetite, dysphagia or food intolerance and eating behavior; every 3 months after the first year	11%
>3 years of attempts to lose weight by lifestyle means	Participants were encouraged to do exercise and maintain a high level of activity	4%
Diet camps, behavioral therapy, and drug therapy	3, 6, and 12 months after surgery by a surgeon; pediatricians and psychologists on a regular basis	10%
NR	NR	0%
NA	NA	NA
Failed conservative treatment	NR	0%
NR	Follow-up visits, no support program	0%
NR	NR	9% for LAGB+RYGB
≥6 months of organized attempts at weight management	Regular visits with the surgeon, psychologist and dietician	NR

Table 2.2 | *continued*

Study	In- and exclusion criteria
Inge et al, 2014 (33)	Pratt (50): BMI ≥35 with major comorbidities and BMI ≥40 with other comorbidities; no binge-purge eating disorders
Lee et al, 2012 (34)	NIH criteria, procedure choice on individual basis
Messiah et al, 2013 (36)	NA (national database)
Miyano et al, 2013 (51)	2002-2006: BMI ≥40 kg/m² with serious obesity-related comorbidities or BMI≥ 50 kg/m² with other comorbidities 2006-2007: BMI ≥35 kg/m² with serious obesity-related comorbidities or BMI ≥40 kg/m² with other comorbidities
Nijhawan et al, 2012 (44)	NR
Olbers et al, 2012 (22)	BMI >40 or BMI >35 kg/m² with comorbidity; pubertal Tanner stage >III and passed peak height growth velocity; no untreated psychiatric disorder
Strauss et al, 2001 (45)	NR
Sugerman et al, 2003 (19)	NIH criteria
Varela et al, 2007 (39)	NA (national database)
Zeller et al, 2009 (20)	Inge: BMI ≥40 with comorbidity or ≥50 (52)
Zeller et al, 2011 (21)	Inge: BMI ≥40 with comorbidity or ≥50 (52)
Sleeve gastrectomy	
Aldaqal et al, 2013 (23)	BMI ≥40 kg/m² with serious obesity-related comorbidities or BMI ≥50 kg/m² with other comorbidities
Alqahtani et al, 2012 (47)	BMI ≥40 or ≥35 kg/m² with comorbidities (5 patients with BMI <35)
Boza et al, 2012 (48)	NIH criteria, evaluation by multidisciplinary team
Inge et al, 2014 (33)	Pratt (50): BMI ≥35 with major comorbidities and BMI ≥40 with other comorbidities; no binge-purge eating disorders
Lennertz et al, 2013 (35)	CAADIP 2010 and IFSO guidelines, procedure choice on individual basis
Nadler et al, 2012 (49)	NIH criteria
Varela et al, 2007 (39)	NA (national database)

NA=not applicable, NR=not reported. NIH, CAADIP, IFSO criteria: BMI ≥40 kg/m² or BMI ≥35 kg/m² with associated comorbidities (53-55); IPEG guideline: BMI ≥35 kg/m² with severe comorbidities or BMI ≥40 kg/m² with other comorbidity (10)

Intervention before surgery	Support after surgery	Loss to follow-up
NR	NR	NR
Exercise and diet with nutritionist, educational sessions and psychological and nutritional evaluations	NR	84% (24 months)
NA	NA	12% – 34% – 63% (3 – 6 – 12 months)
≥6 months of organized attempts at weight management	Regular visits with the surgeon, psychologist and dietician	NR
NR	Follow-up visits, encourage support groups	20%
Multi-disciplinary lifestyle intervention	Follow-up visits, no support program	0%
Serious attempts at weight loss in diet and behavior modification programs	NR	10%
NR	NR	3.1% - 6.7% - 22.2% - 33.3% (1– 5–10–14 years)
NA	NA	NA
Inge: ≥6 months of organized attempts at weight management	NR	10% (12 months)
Inge: ≥6 months of organized attempts at weight management	NR	12%
>6 months of recognized, medically supervised weight loss attempts	NR	NR
6 months in a formal weight loss program	Follow-up visits	17% – 14% (12 – 24 months)
NR	NR	13% – 17% (12 – 24 months)
NR	NR	NR
NR	Multidisciplinary approach including a pediatrician, child psychologist, surgeon and the primary care provider	53% (LSG+LAGB)
NR	Follow-up visits, no program	19% – 0% (6 – 12 months)
NA	NA	NA

Risk of bias within studies

The study design (RCT, prospective, retrospective) and study characteristics are presented in Table 2.1. Potential introducers of bias, other than design, are reported in Table 2.2. of eighteen LAGB studies, seven were prospective, including the only RCT in this review. Five of thirteen RYGB studies were prospective and three of seven LSG studies.

Results of individual studies

In fifteen of the twenty-two included datasets, SD of BMI loss was not reported or available. Nine of the contacted research groups were willing to supply data on BMI loss with SD at one or more follow-up moments to complete the dataset. Finally, 14 SDs were available and 8 were derived as stated in the methods.

Synthesis of results

Per procedure, a short summary is provided of weight loss, complications, comorbidity reduction and QOL. An overview is provided in Tables 2.3, 2.4 and 2.5, and in Figure 2.3.

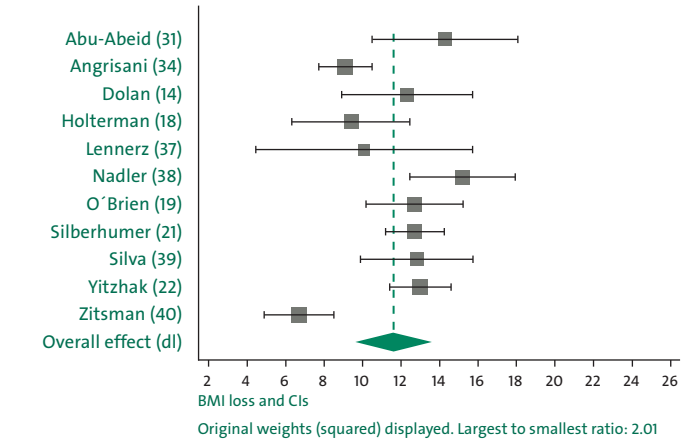
Laparoscopic adjustable gastric band

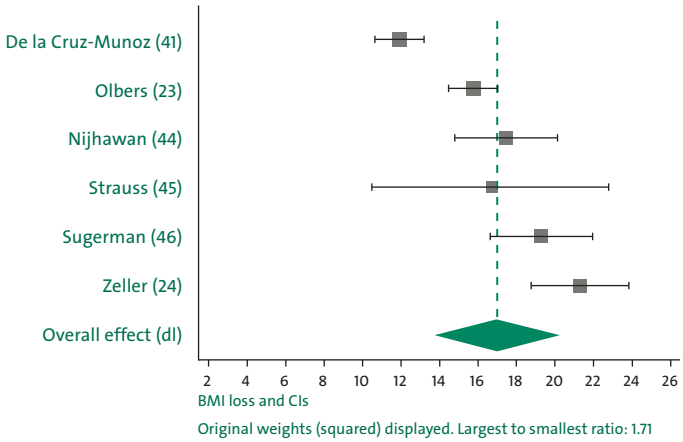
Weight loss

Summary BMI measure at baseline was 45.8 (44.0–47.7) kg/m². The summary effect measure of BMI loss in nine studies was 11.6 (9.8–13.4) kg/m² (Figure 2.3). After the first 12 months, there was no association between length of follow-up and excess BMI loss (ß=0.06, p=0.51). Clustering datasets by banding technique showed no differences in BMI loss (pars flaccida vs. perigastric: 11.0 vs. 10.1 kg/m², p=0.61).

Complications

Thirteen studies report unique data on complications after gastric banding in a total of 538 patients (Table 2.4). No deaths occurred in any of the studies. Perioperative complications including intra-abdominal bleeding and conversion to laparotomy were reported in 0.8% and surgical site infection in 1.4%. Late complications including bowel obstruction and abdominal wall hernia were reported in 1.1% of cases. During the total follow-up period (0 to 138 months) 10.5% of subjects experienced band-related complications (55/524) and 9.9% (17/172) gastrointestinal complaints (nausea, vomiting, GERD, diarrhea and gallstones). There were 77 reinterventions (14.7%), including 3 cholecystectomies. The majority were band-related procedures like replacement or repositioning (n=28), removal (n=12) and port-revision (n=16). Vitamin deficiencies





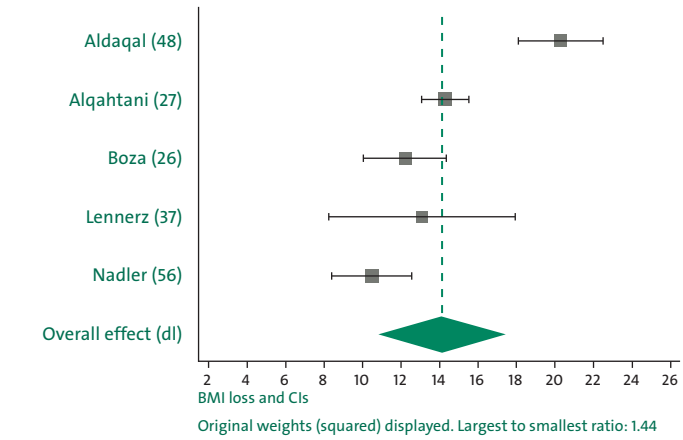


Figure 2.3 | *Forest-plot for BMI loss with 95% confidence intervals and summarized means after LAGB, RYGB and LSG.*

Study	N (at FU)	FU (months)	BMI baseline	SD	BMI loss	SD
Gastric banding						
Perigastric technique						
Abu-Abeid (27)	11	23	46.4	NR	14.3[M]	NR
Angrisani (30)	37	36	46.1	6.31	9.1[A]	4.2
Dolan (31)	9	24	42.6	6.7	12.3[M]	5.2
Holterman (14)	12	18	50	10	9.4[M]	5.4
Pars flaccida technique						
Lennerz (35)	10	12	48.1	9.8	10.1[M]	9.1
Nadler (37)	47	12	47.6	7	15.2[A]	9.7
O'Brien (15)	24	24	42.3	6.1	12.7[M]	NR
Silberhumer (17)	48	36	45.2	7.6	12.7[A]	5.4
Silva (38)	12	36	46.1	11.8	12.8[A]	5.2
Yitzhak (18)	60	39.5	43	NR	13[M]	NR
Zitsman (40)	47	12	50 (M) 48.1 (F)	NR	6.7[M]	NR
Gastric bypass						
De la Cruz-Munoz (41)	71	9-15	46.2	5.1	11.3[A]	5.7
Nijhawan (44)	20	85.8	45.7	NR	17.1[M]	NR
Olbers (22)	81	24	45.5	6.0	15.3[A]	6.0
Strauss (45)	10	68.8	52.4	10.1	16.2[C]	10.3
Sugerman (19)	20	60	52	11	19[M]	NR
Zeller (20)	14	24	59.9	8.7	21.1[A]	5.1
Sleeve gastrectomy						
Aldaqal (23)	32	12	49.6	4.9	20.3[M]	NR
Alqahtani (47)	76	6	49.6 (median)	11.5 (IQR)	14.3[A]	5.5
Boza (48)	34	24	38.5	3.7	12.2[M]	NR
Lennerz (35)	11	12	51.8	8.3	13.1[M]	8.2
Nadler (56)	13	6	52	9	10.5[A]	3.8

Table 2.3 | *BMI loss data used for meta-analysis; male (M), female (F); from manuscript [M]; from author [A]; calculated from individual data [C]*

were reported in 5 of 18 studies; oral supplements for iron, vitamin D, folic acid and zinc deficiencies were prescribed in 0.5 to 36% of patients, but criteria for deficiencies were poorly defined. Only 2 of 18 studies report standard postoperative vitamin supplementation, while 13 do not mention a standard policy.

Resolution of comorbidities

Out of the 18 LAGB studies included in this review, 11 report data on comorbidity resolution (Table 2.5). The definitions and cut-off values for comorbidities were specified in 5 of 11 studies and varied between studies. Resolution rates for hypertension, reported in nine studies, range from 22.9 to 100%; six studies showed complete resolution in all patients. Nine studies report prevalence of dyslipidemia in 8 to 86%, with eight reporting resolution in 0 to 100% (median 50%) of all cases. Six out of seven studies that report on diabetes prevalence in 0 to 33%, all showed 100% resolution after surgery. Resolution of pre-diabetes (3 studies, prevalence 24–93%) ranged from 72 to 100%.

Quality of life

Holterman et al. showed that 75% of the children had abnormal scores on the Pediatric Quality of Life Inventory (Peds-QL) at baseline, which improved at 12 and 18 months after surgery (14). The RCT by O'Brien et al. (15) showed improvements in reported physical functioning, general health, self-esteem, family activities and change in health with the Child Health Questionnaire (CHQ CF-50) after gastric banding, while the lifestyle group improved only in general health perception. Silberhumer et al. (16, 17) found significant improvement after 35 months by using the BAROS and Moorehead-Ardelt Quality of Life questionnaires but no further changes between 3 and 5 years after surgery. Yitzhak et al. (18) report 93% improvement in physical activity and 72% improvement in social- and self-esteem with non-validated questionnaires.

Pars flaccida vs. perigastric technique

The LAGB related problems including slippage, pouch dilation and migration – after a follow-up period of 0–7 years – does not appear to occur more in patients who were operated before the surgeons updated their techniques to the currently used pars flaccida technique (11.2% (10/89) vs. 10.3% (45/435)).

Table 2.4 | *Complications*

Authors	N	FU	Complication					
			Death	Perioperative complications	Surgical site infection	Late complications	Hiatal hernia	Band-specific
LAGB								
Perigastric								
Abu-Abeid et al, 2003	11	6 - 36 m	*	0	*	0	*	0
Angrisani et al, 2005	58	0 - 7 y	0	1	*	*	*	6
Holterman et al, 2010	20	15 - 42 m	*	*	*	*	1	4
Pars flaccida								
Alqahtani, 2011	50	NR - 5 y	*	0	*	*	*	2
Fielding et al, 2005	41	1 – 70 m	0	0	*	*	*	2
Lee et al, 2012	23	1 - 24 m	*	*	*	*	*	2
Nadler et al, 2008	73	12 – 24 m	0	*	1	1	3	7
O'Brien et al, 2010	24	24 m	*	0	*	*	*	8
Silberhumer et al, 2011	50	63 – 138 m	*	*	*	*	*	6
Silva et al, 2012	14	12 – 36 m	0	0	*	*	*	2
Yitzhak et al, 2006	60	25 – 65 m	0	0	*	*	*	10
Zitsman et al, 2011	100	12 m	0	1	*	1	1	6
Inge et al, 2014	14	30 d	0†	1	0†	0†	*†	*†
TOTAL	**538**		**0% (0/346)**	**0.8% (3/372)**	**1.4% (1/73)**	**1.1 % (2/184)**	**2.6% (5/193)**	**10.5% (55/524)**
Short-term perioperative outcome								
Varela et al, 2007	90	30 d	0	*	*	*	*	*
RYGB								
De la Cruz–Munoz et al	71	9 – 15 m	*	0	*	*	*	*
Inge et al, 2004	10	1 m – 2 y	*	1	*	3	*	*
Lee et al, 2012	32	1 – 24 m	*	*	*	1	*	*

					Intervention									
Gastrointestinal complaints	Nutritional deficiency / dehydration	DVT	Pulmonary system (pneumonia, pulmonary embolism)	Total	Conversion to malabsorptive anatomy	Band, removal	Band replacement / repositioning	Band, port revision	Gastrointestinal obstruction	Leak/fistula repair	Cholecystectomy	Abdominal hernia repair	EGD	Total
0	*	*	*	0	*	*	*	*	*	*	*	*	*	0
*	*	*	*	7	3	5	3	*	*	*	*	*	*	11
*	*	*	*	5	*	*	1	3	*	*	*	1	*	5
9	1	*	*	12	*	2	*	*	*	*	*	0	*	2
*	*	*	*	2	*	*	1	1	*	*	*	*	*	2
*	*	*	*	2	*	1	1	*	*	*	*	*	*	2
5	*	*	*	17	*	2	5	1	*	*	1	3	*	12
1	*	*	*	9	*	*	6	2	*	*	1	*	*	9
*	*	*	*	6	8	*	2	2	*	*	*	*	*	12
2	*	*	*	4	*	*	*	2	*	*	1	*	*	3
*	*	*	*	10	*	2	6	2	*	*	*	*	*	10
*	*	*	*	9	*	*	3	3	2	*	*	1	*	9
1†	*†	0†	1†	3†	*	*	*	*	0	*	*	0	*	0†
9.9% (17/172)	**2% (1/50)**	*	*	**83**	**11**	**12**	**28**	**16**	**2**	**0**	**3**	**5**	**0**	**14.7% (77/524)**
*	*	*	*	0	*	*	*	*	*	*	*	*	*	0
2	*	*	*	2	*	*	*	*	*	*	*	*	*	0
1	1	1	*	7	*	*	*	*	*	1	*	*	1	2
*	1	*	*	2	*	*	*	*	*	1	*	*	*	1

Table 2.4 | *continued*

Authors	N	FU	Complication					
			Death	Perioperative complications	Surgical site infection	Late complications	Hiatal hernia	Band-specific
Miyano et al, 2013	77	90 d	0	2	2	24	*	*
Nijhawan et al, 2012	20	60 – 120 m	0	0	1	3	*	*
Olbers et al, 2012	81	24 m	0	2	*	6	*	*
Strauss et al, 2001	10	8 – 156 m	*	0	*	2	*	*
Sugerman et al, 2003	33	1 – 14 y	2	*	5	14	*	*
Inge et al, 2014	161	30 d	0†	17	3†	9†	*†	*†
TOTAL	**495**		**0.9% (2/211)**	**5.1% (22/430)**	**6.2% (8/130)**	**20.2% (53/263)**	*	*
Short-term perioperative outcome								
Varela et al, 2007	191	30 d	0	*	*	*	*	*
LSG								
Aldaqal et al, 2013	32	12 m	*	0	*	*	*	*
Alqahtani et al, 2012	99	6 – 24 m	0	0	2	1	*	*
Boza et al, 2012	51	6 – 24 m	0	0	*	1	*	*
Nadler et al, 2012	23	9 – 15 m	*	0	*	0	*	*
Inge et al, 2014	67	30 d	0†	2	2†	3†	*†	*†
TOTAL	**272**		**0 % (0/150)**	**0.7% (2/272)**	**2.0% (2/99)**	**1.2% (2/173)**	*	*
Short-term perioperative outcome								
Varela et al, 2007	28	30 d	0	*	*	*	*	*

*Complications: death (all cause), perioperative (conversion, bleeding, organ laceration), surgical site infection, late complications (obstruction, abscess, internal hernia, leak, incisional hernia), hiatal hernia, band-specific (port revision, slippage, dilated pouch, band migration), gastrointestinal complaints (nausea, vomiting, intestinal blood loss, diarrhea, GERD, gallstones, dumping), nutritional deficiency/ dehydration, DVT, pneumonia/pulmonary embolus. *not reported; † not summarized due to short follow-up*

						Intervention									
Gastrointestinal complaints	Nutritional deficiency / dehydration	DVT	Pulmonary system (pneumonia, pulmonary embolism)	Total	Conversion to malabsorptive anatomy	Band, removal	Band replacement / repositioning	Band, port revision	Gastrointestinal obstruction	Leak/fistula repair	Cholecystectomy	Abdominal hernia repair	EGD	Total
*	5	1	0	34	*	*	*	*	4	4	*	2	13	23
*	*	*	1	5	*	*	*	*	2	0	*	*	1	3
11	*	*	*	19	*	*	*	*	5	0	5	2	*	12
2	1	*	*	5	*	*	*	*	1	*	2	1	*	4
*	1	*	1	22	2	*	*	*	1	*	*	6	3	12
*†	*†	1†	2†	17†	*	*	*	*	3	4	*	*	3	10†
9.3% (16/172)	**5.6% (9/162)**	**2.3% (2/87)**	**1.5% (2/130)**	**96**	**2**	**0**	**0**	**0**	**13**	**6**	**7**	**11**	**18**	**17.1% (57/334)**
*	*		*	4.3-7.6%	*	*	*	*	*	*	*	*	*	0
*	*		*	0	*	*	*	*	*	*	*	*	*	0
3	*		*	6	*	*	*	*	*	*	*	*	*	0
*	*		*	1	*	*	*	*	*	1	*	*	1	2
3	*		*	3	*	*	*	*	*	*	*	*	*	0
2†	1†		1†	11†	*	*	*	*	0	2	*	0	*	2†
4.9% (6/122)	*		*	**10**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**1.0% (2/205)**
*	*		*	0	*	*	*	*	*	*	*	*	*	0

Table 2.5 | *Comorbidity prevalence and reduction*

Author		HT	Dyslipidemia
LAGB			
Abu-Abeid et al, 2003 (27)	Baseline N (%)	NR	2/11 (18.2%)†, 1/11 (9.1%)‡
	Resolved N (%)	NR	2/2 (100%)†, 0/1 (0%)‡
Al-Qahtani et al, 2007 (28)	Baseline N (%)	6/51 (11.8%)	NR
	Resolved, N (%)	6/6 (100%)	NR
Angrisani (30)	Baseline N (%)	8/58 (13.4%)	6/58 (10.3%)
	Resolved N (%)	NR	NR
Fielding et al, 2005 (32)	Baseline N (%)	2/41 (4.9%)	NR
	Resolved N (%)	2/2 (100%)	NR
Holterman et al, 2010 (14)	Baseline N (%)	9/20 (45%)	16/20 (80%)
	Resolved N (%)	9/9 (100%)	11/16 (67%)
Lee et al, 2012 (34)	Baseline N (%)	2/23 (9%)	2/23 (9%)‡
	Resolved N (%)	NR	1/2 (50%)
Messiah et al, 2013 (36)	Baseline N (%)	80 (18%)	61 (14%)
	Improved N (%)	54%	23%
Nadler et al, 2008 (37)	Baseline N (%)	4/21 (19%)	7/21 (33%)
	Resolved N (%)	4/4 (100%)	3/7 (43%)
Silberhumer et al, 2011 (17)	Baseline N (%)	12/50 (24%)	4/50(8%)
	Resolved, N (%)	11/12 (91.7%)	4/4 (100%)
Silva et al, 2012 (38)	Baseline N (%)	13/14 (92%)	12/14 (85.7%)
	Resolved, N (%)	13/13 (100%)	8/12 (66.7%)
Yitzhak et al, 2006 (18)	Baseline N (%)	3/60 (5%)	NR
	Resolved, N (%)	3/3 (100%)	NR
Zitsman et al, 2011 (40)	Baseline N (%)	35/85 (41.2%)	49/85 (57.6%)
	Resolved, N (%)	8/35 (22.9%)	24/49 (49%)
RYGB			
Miyano et al, 2013 (51)	Baseline N (%)	18 (29%)	38 (62%)
	Resolved, N (%)	NR	NR
Inge et al, 2004 (42)	Baseline N (%)	NR	NR
	Resolved, N (%)	NR	NR
Lee et al, 2012 (34)	Baseline N (%)	Jun 32	2/32 (6%)
	Resolved, N (%)	NR	2/2 (100%)‡

T2DM	Pre-diabetes / Insulin resistance	OSAS	Musculoskeletal complaints	Asthma	Menstrual problems	GERD
NR	NR	NR	NR	NR	2/11 (18.2%)‡	NR
NR	NR	NR	NR	NR	2/2 (100%)‡	NR
7/51 (13.7%)	NR	10/51 (19.6%)	7/51 (13.7%)†	NR	NR	NR
7/7 (100%)	NR	10/10 (100%)	7/7 (100%)†	NR	NR	NR
8/58 (13.4%)	NR	10/58 (17.2%)	12/58 (20.7%)†	NR	4/58 (69%)‡	NR
NR	NR	NR	NR	NR	NR	NR
2/41 (4.9%)	NR	1/41 (2.4%)	1/41 (2.4%)‡	NR	NR	NR
2/2 (100%)	NR	1/1 (100%)	1/1 (100%)‡	NR	NR	NR
NR	18/20 (90%)†	NR	NR	NR	NR	NR
NR	13/18 (72%)†	NR	NR	NR	NR	NR
0/23 (0%)	NR	3/23 (13%)	NR	NR	NR	NR
0/0	NR	NR	NR	NR	NR	NR
65 (15%)	NR	80 (18%)	113 (25%)¥ 90 (21%) #	84 (19%)	50 (11%) † 45 (10%) ¥	109 (25%)
59%	NR	46%	50% ¥ 44% #	23%	38% † 31% ¥	45%
NR	5/21 (24%)◊	4/21 (19%)	10/21 (48%) ¥, 5/21 (24%)†	NR	NR	1/ 21 (5%)
NR	5/5 (100%)◊	3/4 (75%)	7/10 (70%)¥, 3/5 (60%)†	NR	NR	1/1 (100%)
5/50 (10%)	NR	NR	8/50 (16%)§	3/50 (6%)	NR	1/50 (2%)
5/5 (100%)	NR	NR	7/8 (87.5%)§	3/3 (100%)	NR	1/1 (100%)
NR	13 /14 (92.8%)†	NR	NR	NR	NR	NR
NR	13/13 (100%)†	NR	NR	NR	NR	NR
2/60 (33.3%)	NR	10/60 (16.7%)	NR	3/60 (%)	NR	NR
2/2 (100%)	NR	10/10 (100%)	NR	3/3 (100%)	NR	NR
NR	NR	NR	NR	28/85 (32.9%)	26/85 (31%)†¥	NR
NR	NR	NR	NR	4/28 (14.3%)	21/26 (81%)†¥	NR
8 (13%)	NR	46 (69%)	NR	11 (21%)	11 (24%) ¥	15 (27%)
NR	NR	NR	NR	NR	NR	NR
1/10 (10%)	NR	1/10 (10%)	NR	NR	NR	NR
1/1 (100%)	NR	1/1 (100%)	NR	NR	NR	NR
3/32 (%)	NR	Mai 32	NR	NR	NR	NR
3/3 (100%)	NR	NR	NR	NR	NR	NR

Table 2.5 | *continued*

Author		HT	Dyslipidemia
Messiah et al, 2013 (36)	Baseline N (%)	118 (26%)	65 (14%)
	Improved N (%)	61%	59%
Nijhawan et al, 2012 (44)	Baseline N (%)	3/25 (12%)	10/25 (40%)
	Resolved, N (%)	3/3 (100%)	10/10 (100%)
Olbers et al, 2012 (22)	Baseline N (%)	0/81 (0%)	15/80 (19%)†; 27/81 (33%)◊
	Resolved, N (%)	N/A	14/15 (93.3%)†; 15/27 (55.5%)◊
Strauss et al, 2001 (45)	Baseline N (%)	3/10 (30%)	NR
	Resolved /improved, N (%)	3/3 (100%)	NR
Sugerman et al, 2003 (19)	Baseline N (%)	11/33 (33%)	NR
	Resolved, N (%)	9/11 (82%)	NR
LSG			
Aldaqal et al, 2013 (23)	Baseline N (%)	4/32 (13%)	NR
	Resolved, N (%)	3/4 (75%)	NR
Alqahtani et al, 2012 (47)	Baseline N (%)	39/108 (36.1%)	52/108 (48.1%)
	Resolved, N (%)	27/36 (75%)	21/30 (70%)
Boza et al, 2012 (48)	Baseline N (%)	4/51 (7.8%)	12/51 (23.5%)
	Resolved, N (%)	4/4 (100%)	7/12 (58%)
Nadler et al, 2012 (57)	Baseline N (%)	1/7 (14.3%)	NR
	Resolved, N (%)	1/1 (100%)	NR

Dyslipidemia including: † elevated triglycerides, ‡ elevated total cholesterol or ◊ elevated LDL.

Pre-diabetes or insulin resistance defined as: † HOMA insulin resistance, ◊ impaired glucose tolerance, ¥ elevated fasting glucose, or ‡ elevated fasting insulin.

Musculoskeletal problems defined as: † osteoarthropathy, ‡ Perthes disease of the hip, ¥ back pain, # musculoskeletal disorder, § orthopedic comorbidities/pain or ◊ compression fracture of vertebrate.

Menstrual problems including: † menstrual irregularity, ‡ amenorrhoea or ¥ polycystic ovary syndrome.

HT=hypertension; T2DM=type 2 diabetes mellitus; OSAS=obstructive sleep apnea syndrome; GERD=gastro esophageal reflux disease.

T2DM	Pre-diabetes / Insulin resistance	OSAS	Musculoskeletal complaints	Asthma	Menstrual problems	GERD
67 (15%)	NR	117 (26%)	162 (36%) ¥, 127 (28%) #	94 (21%)	85 (18%) †, 41 (9%) ¥	127 (28%)
79%	NR	56%	50% ¥, 44% #	40%	38% †, 31% ¥	62%
3/25 (12%)	NR	4/25 (16%)	14/25 (56%)†	6/25 (24%)	NR	5/25 (20%)
3/3 (100%)	NR	4/4 (100%)	13/14 (92.9 %)†	6/6 (100%)	NR	4/5 (80%)
1/81 (1.2%)	17/78 (21%)¥; 55 / 78 (70%)‡	0/81 (0%)	NR	NR	NR	NR
1/1 (100%)	13/17 (76.5%)¥; 53/55 (96%)‡	N/A	NR	NR	NR	NR
NR	NR	2/10 (20%)	1/10 (10%)◊	NR	NR	NR
NR	NR	2/2 (100%)	1/1 (100%)◊	NR	NR	NR
2/33 (6%)	NR	6/33(18%)	11/33 (33%)	NR	NR	5/33 (15%)
2/2 (100%)	NR	6/6 (100%)	4/11 (36%)	NR	NR	3/5 (60%)
5/32 (16%)	NR	1/32 (3%)	NR	NR	NR	NR
4/5 (80%)	NR	1/1 (100%)	NR	NR	NR	NR
22/108 (20.4%)	14/108 (13%)¥ or ◊	36/108 (33.3%)	NR	NR	NR	NR
15/16 (93.8%)	11/11 (100%)¥ or ◊	20/22 (90.9%)	NR	NR	NR	NR
2/51 (3.9%)	27/51 (52.9%)†	NR	3/51 (5.9%)†	NR	NR	NR
1/2 (50%)	26/27 (96.2%)†	NR	N/A	NR	NR	NR
NR	3/7 (%)†	4/7 (57%)	1/7 (14.3%)§	1/7 (14.3%)	1/7 (14.3%)¥	1/7 (14.3%)
NR	3/3 (100%)†	4/4 (100%)	1/1 (100%)§	1/1 (100%)	1/1 (100%)¥ improved	1/1 (100%) improved

Roux-en-Y gastric bypass

Weight loss

The studies reporting on laparoscopic Roux-en-Y gastric bypass have a summary BMI loss of 16.6 kg/m² (13.4–19.8) after 12 to 86 months (Table 2.3, Figure 2.2). A follow-up period exceeding 12 months was not correlated to BMI loss (ß=0.04, p=0.51). BMI loss after RYGB was significantly higher than after LAGB (p=0.008). Mean pre-operative BMI was 49.6 (46.4–52.7) kg/m² and did not differ from LAGB (p=0.11).

Complications

Nine studies present summarizable complication rates in a total of 495 patients. Two sudden deaths were reported in one study, 2 and 6 years after surgery respectively, which were probably unrelated to the procedure. However, no autopsies were performed to determine the cause of death (19). Perioperative complications including anastomotic leakage, bleeding and conversion occurred in 5.1% and infection of the surgical site in 6.2% of patients. Late complications including obstruction, internal herniation, ulcers and abdominal wall hernia occurred in 20.2% of patients.

Gastrointestinal complaints like nausea, vomiting, dumping and GERD were reported in 9.3%, nine patients in five studies (5.6%) suffered from nutritional deficiencies or dehydration requiring hospitalization. Less severe vitamin deficiencies were reported in 6 of 13 studies; oral supplements for iron, vitamin A, vitamin B1, vitamin B12, vitamin D, folic acid and zinc deficiencies were used in an estimated 4–56% of patients, but criteria for deficiencies and exact numbers were poorly described. In 5 of 13 studies postoperative vitamin supplementation was standard policy, while in 7 no details are provided. The highest percentage of deficiencies occurred in the study in which no supplements were supplied.

Fifty-seven reinterventions (17.1%) were performed including cholecystectomy in seven, endoscopic procedures (mainly balloon dilation for stricture of the anastomosis) in eighteen, surgery for gastrointestinal obstruction in thirteen and for leak or fistula repair in six.

Resolution of comorbidities

Eight of the thirteen studies on RYGB report data on comorbidity resolution and/or improvement (Table 2.5). The definitions and cut-off values for comorbidities were specified in 5 of 8 studies and varied between studies. The studies reporting on hypertension (n=4) show 61 to 100% improvement or resolution. 6–62% of the subjects had dyslipidemia, resolving in 56 to 100%. Diabetes resolved in 79 to 100%, with resolution in all subjects in 5 out of 6 studies.

Quality of life

Quality of life, reported in two studies, showed significant improvement in seven of the eight health domains on the Short Form-36 Health Survey (SF-36) at 1 year follow-up, and significantly increased quality of life scores after 6 months, but not after 12 (assessed with the PedsQL and IWQOL-Kids) . Depression scores were significantly less, 6 and 12 months after surgery, than before surgery (20-22).

Laparoscopic sleeve gastrectomy

Weight loss

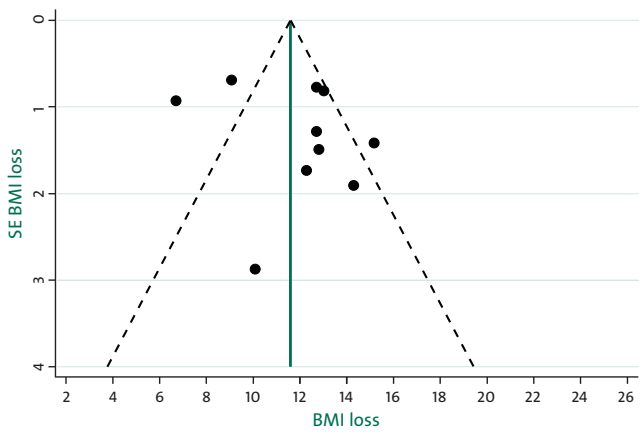
Five studies present the results of the relatively new LSG technique with a follow-up between 6 and 24 months. BMI before surgery was 48.1 (41.8–54.5) kg/m², which does not differ from LAGB or RYGB patients (p=0.42 and p=0.50 respectively). BMI loss in these studies is 14.1 (10.8–17.5) kg/m² and does not differ from LAGB and RYGB (p=0.17 and p=0.24 respectively).

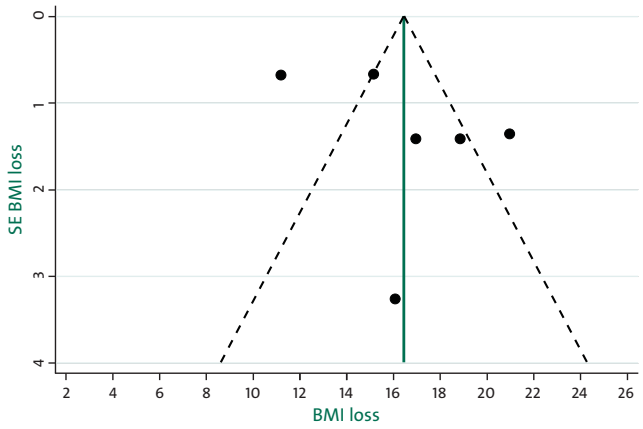
Complications

Five studies including 272 patients reported two perioperative complications (0.7%) and no mortality. Incidence of wound infection was 2.0% and late complications occurred in 1.2%, gastrointestinal complaints in 4.9% (Table 2.4). Postoperative vitamin supplementation was described in one of seven studies; none of the studies report whether deficiencies occurred.

Resolution of comorbidities

In four out of five studies on LSG, comorbidities are reported (Table 2.5). The definitions and cut-off values for comorbidities were specified in 2 of 4 studies and varied between studies. Hypertension resolved in 75–100%. Dyslipidemia improved, with resolution rates of 58% to 70% and diabetes, reported in three studies, resolved in 50% to 93.8%.





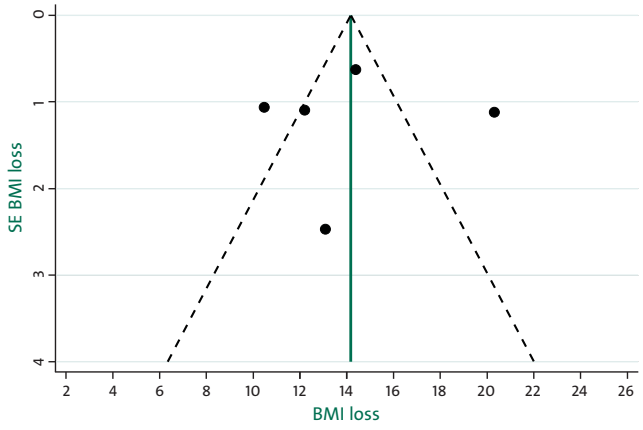


Figure 2.4 | *Funnel plots of SEM of BMI loss versus BMI loss for assessment of heterogeneity in outcome reporting. Dots outside the 95% pseudo confidence limits are indicative of heterogeneity.*

Quality of life

Aldaqal et al. assessed self-esteem and quality of life at baseline and one year after LSG with the Rosenberg self-esteem scale (RSE) and the Pediatric Quality of Life Inventory (Peds-QL) (23). Patients improved significantly on the RSE and all 6 scores of the Peds-QL (including the summary score) one year after the procedure.

Risk of bias across studies

Figure 2.4 shows the funnel plots for standard error of BMI loss against BMI loss in each procedure. Eight of the studies reporting on LAGB outcome are within the expected range, while one study shows more and two show less than expected BMI loss. Four RYGB studies are in the expected range, while two are not (one more, one less) and three LSG studies are in the expected range, while two are not (one more, one less).

DISCUSSION

Summary of evidence

The 37 studies that were eligible for systematic reviewing represent the increasing interest in bariatric surgery in morbidly obese adolescents, although the studies were mainly observational and varied in quality. To ensure that the meta-analysis was based on valid data and solidly compares surgical methods, we reported only peer reviewed published studies and obtained additional data from the authors of nine studies.

All three procedures lead to significant weight loss in morbidly obese adolescents and similar to a large Swedish study in adults, weight loss is most pronounced after RYGB (9). This seems to persist after both RYGB and LAGB. For LSG studies long-term follow-up is not yet available. While adverse events are relatively mild and long-term complication rates are acceptable, they are more frequent and more serious after RYGB than after LAGB. In the currently available follow-up after LSG the rate of adverse events appears to be similar to that after LAGB. Although a healthy nutritional status in adolescents is important to prevent developmental and growth deficiencies, standard postoperative vitamin supplementation regimens and occurrence of deficiencies are not reported in most studies (not at all in LSG studies). However, more, and more severe deficiencies occur after RYGB than after LAGB.

Reduction of comorbidity, which is pivotal for health gain, is impressive in all techniques and QOL consistently showed improvement, although follow-up up to 24 months may not be enough to capture negative long-term effects in life after bariatric surgery. The difference in adults between adverse events of the old perigastric LAGB technique and the more recently adapted pars flaccida technique (24) is not reproduced reviewing young patients.

Limitations

Funnel plots show heterogeneity of the data but no indication of publication bias due to underreporting of poor outcomes. A limitation of the currently available literature is the lack of high quality, prospective randomized controlled trials, which increases the risk of bias and therefore introduces heterogeneity. Assessment of the three fundamental domains in risk of bias in observational studies (appropriate selection of participants, appropriate measurement of variables and appropriate control of confounding) shows that studies are heterogeneous in patient selection, in pre- and postoperative treatment protocol and that loss-to follow-up is substantial. Furthermore,

reduction of comorbidity receives sufficient attention in most studies, but varying and lacking definitions of comorbidity introduce another possible source of bias. The similarity in outcome in all studies however strengthens our conclusion that the current methods of summarizing BMI loss, complication rate and reduction of comorbidity are indicative of the true outcome.

Conclusions

This review is the first that has retrieved sufficient data for meta-analysis of BMI loss by contacting all authors of included studies, to enable a solid statistical analysis. All three analyzed bariatric surgical techniques - laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy - result in substantial weight loss and improvement of comorbidity in the short to medium term. This indicates that, considering the acceptable complication rate, surgical intervention is applicable in appropriately selected adolescents. While BMI loss after RYGB is superior, a higher rate of adverse events and reinterventions has to be taken into account. We recognize that RYGB is currently considered in the treatment of adolescents with a more extreme BMI (>50 kg/m²), while LAGB and LSG are applied when obesity is less extreme.

The quality of the available literature is limited. In the current climate where availability of bariatric surgery for morbidly obese children is already increasing, randomized controlled trials comparing bariatric surgery with standard conservative treatment are difficult to perform. Currently seven active studies are registered in ClinicalTrials.gov assessing the effects of bariatric surgery in adolescents, including one randomized controlled trial. We recommend the involved researchers to use solid outcome reporting strategies and strongly support the pleas for standardized weight loss reporting (25, 26).

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Obesity Facts. 2016

Long-Term Follow-Up is Essential to Assess Outcome of Gastric Banding in Morbidly Obese Adolescents: A Retrospective Analysis

ABSTRACT

BACKGROUND

Adolescent obesity is rapidly becoming more prevalent and is associated with chronic health conditions and psychosocial morbidity. Lifestyle intervention is often ineffective in morbidly obese adolescents, and bariatric surgery is gradually becoming an accepted treatment. However, little is known about long-term results.

METHODS

Hospital charts of patients who had undergone gastric banding more than 5 years ago at an age of 18 years or younger, were retrospectively analyzed. Weight loss, complications, reoperations, and comorbidity reduction were assessed as well as health status, food behavior, and personality.

RESULTS

BMI loss in 10 adolescents was 10.7 kg/m² *(–0.9 to 12.9 kg/m²)* after a median follow-up of 64 months *(52–84 months)*; the major part of weight loss occurred after the first year. In 4 patients the gastric band was removed after 3.5–5.5 years. Two out of 3 patients effectively lost weight after conversion to a bypass type procedure. One patient is maintaining a stable healthy weight after band removal.

CONCLUSIONS

Laparoscopic adjustable gastric banding in morbidly obese adolescents had a failure rate of 40%, but was a successful therapy in the other 60% without major adverse events. Follow-up longer than 36 months was crucial for optimal evaluation of weight loss and reoperation rate.

INTRODUCTION

An estimated 13.0% of US adolescents are currently morbidly obese; a number that has impressively tripled over the past decade (1). Obesity is associated with chronic health conditions including type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea syndrome, and osteoarthritis (2, 3). Furthermore, obese adolescents are likely to suffer from psychological morbidity, loss of self-esteem, and social exclusion (4). Management of adolescent obesity is mostly focused at combined lifestyle intervention, initiated and coordinated by specialized pediatricians. While often effective in the short term, long-term effects are disappointing, especially in extreme obesity. A Cochrane review published in 2009 shows a maximum of 1.7 kg/m² BMI loss after 12 months (5).

Bariatric surgery is becoming an accepted treatment for weight reduction in morbidly obese adolescents. Presently, three operative techniques are commonly used: laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (RYGB), and laparoscopic sleeve gastrectomy. These techniques differ in excess weight loss, resolution of comorbidity, quality of life improvement, and complication rate (6). The short-term results are relatively well documented, but medium and long-term effects are largely unknown while studies in adults show that reoperation mostly occurs several years after bariatric surgery (7). In our hospital LAGB was done in adolescents until 2008, when the Health Care Inspectorate (Inspectie voor de Gezondheidszorg; IGZ), based on a new national guideline on obesity, asked for more evidence-based practice and prohibited adolescent bariatric surgery. To assess the medium-term results of LAGB we analyzed the outcome of 10 adolescents who underwent this procedure more than 5 years ago.

The aim of this study is to assess long-term weight loss, adverse events, comorbidity resolution, and health status in morbidly obese adolescents operated on before 2008. The secondary aim is to evaluate the available data on eating behavior and personality traits before and after surgery (8–11).

MATERIAL AND METHODS

The hospital registration system was queried for all patients aged 18 years or younger who had surgery coded as LAGB. All patients were operated in or before 2008, when the IGZ prohibited bariatric surgery in adolescents in non-research settings. The medical ethics committee of the Maastricht University Medical Center waived the acqui-

sition of informed consent (METC 14–4-122). Patients were eligible for surgery if non-surgical attempts to lose weight had failed and BMI was above 40 kg/m² or above 35 kg/m² with comorbidity. The procedure was not scheduled before the patient had been assessed by a medical psychologist, primed for the postoperative eating pattern by a dietician and discussed in the multidisciplinary team. The adjustable silicone gastric band (Lap-Band, INAMED Health, Santa Barbara, CA, USA) was placed via laparoscopy using pars flaccida technique in all subjects (12).

Bariatric surgery follow-up included frequent outpatient clinic visits in the first year after surgery and yearly afterwards. Weight loss, vital parameters, comorbidity resolution, and adverse events were evaluated at each visit. The surgeon and dietician evaluated eating pattern and weight loss, and the gastric band was adjusted when indicated. In the past year, all adolescent patients were asked to complete questionnaires to assess their health status, eating behavior, and personality. Data on weight loss, comorbidity, and complications were retrospectively collected from medical records. Weight loss is expressed as BMI loss and as excess BMI loss (a normal BMI corresponds to the age- and sex-adjusted equivalent of 25 kg/m²) at the latest follow-up with gastric band in situ.

Questionnaires

Four validated questionnaires were used to assess health status, eating behavior and personality. The Dutch version of the Short Form 36 Health Survey (SF-36) was used to assess health status in eight domains. Raw scale scores of the SF-36 were transformed into standardized scores from 0 (the worst) to 100 (optimal) and compared to Dutch population reference values (13). The Dutch Questionnaire of Eating Behavior (NVE) assesses eating behavior in three subscales: restrained eating, emotional eating, and external eating (14). Subscale scores are compared to a Dutch normal-weight population in the graph (8). The Eating Disorder Examination Questionnaire (EDE-Q) is a 36-item questionnaire to assess the psychopathology associated with the diagnosis of an eating disorder. It retains four subscales: restraint, eating concern, shape concern, and weight concern. Subscale scores are compared to international population references (15). The Dutch Personality Questionnaire (NPV) assesses personality traits on seven scales: neuroticism, social anxiety, rigidity, hostility, egoism, dominance, and self-esteem (16). Because the NPV is not validated under the age of 16 years, the junior version of the NPV (the NPV-J) was used for those who were younger in preoperative screening. It consists of five scales (of which three are identical to the scales on the adult version): neuroticism, perseverance, social anxiety, recalcitrance, and dominance (17). All questionnaires, except for the SF-36, were also used during the preoperative screening.

Statistical Analysis

Statistical analysis was performed using Prism 6.0 (GraphPad Software, Inc. La Jolla, CA, USA) and SPSS 19.0 (IBM Corporation, Somers, NY, USA). Baseline data were compared with data acquired at the latest visit with the gastric band in situ or with data acquired at the last visit, when appropriate. When patients were lost to follow-up, their last known data were used as end of follow-up. Weight assessment parameters and questionnaire scores are reported as median (interquartile range, IQR). Data were tested with non-parametric Wilcoxon signed rank test, since Gaussian distribution cannot be assumed and missing data at 6 and 12 months impedes multiple comparisons. A p value < 0.05 was considered statistically significant.

RESULTS

Weight Loss, Adverse Events, and Reoperations

Ten adolescents were treated with gastric banding between July 2004 and August 2008. Seven patients visited our clinic in the past year, while the other 3 were lost to follow-up. The presented results represent all 10 patients at their latest follow-up visit. BMI loss with gastric band in situ was 10.7 kg/m² (–0.9 to 12.9 kg/m²) after a median follow-up of 64 months (52–84 months), corresponding to 63.7% (–1.6 to 84.5%) excess BMI loss (Table 3.1 , Figure 3.1). Six patients lost more than 50% excess BMI, one lost 41%, and one lost 7% while 2 patients gained weight despite their gastric band (43% and 27% excess BMI, respectively).

Individual adverse events and reoperations are listed in Table 3.1. Two subjects needed temporary desufflation of the gastric band; one for slippage and one for obstruction (after 2 and 3 years, respectively), after which their complaints resolved. In 4 out of 10 patients the band was removed.

One patient was treated in another bariatric surgery center for persistent referred pain in her left shoulder that resolved with removal of the gastric band. Conversion to biliopancreatic diversion (BPD) 3.5 years afterwards, because of weight regain, was uncomplicated and resulted in loss of 114% of her previous excess BMI. Two years after conversion to BPD this patient was hospitalized for inflammatory disease of the colon with unknown etiology. A second patient had unexplained persistent sensations of dyspnea from postoperative day 1 that resolved with removal of the band 4.5 years later. She regained 10 of the 40 kg she had lost before, but had a stable weight without further intervention at the last visit, more than 1 year after band removal. A third

patient regained 20 of the 35 kg she had lost before, when she underwent uncomplicated conversion to RYGB after 3.5 years and lost exactly 100% of her previous excess BMI. One year later she had an internal hernia that required laparoscopic repair (and revision 1 year later). The fourth patient had her gastric band removed after 5.5 years because of weight regain and is now waiting for RYGB. Other surgical procedures in-

			BMI (kg/m²)					Follow up (months)			
PID	Sex	Age (y)	OR	6M	12M	End*	%EBMIL	LAGB*	Total**	Adverse events (therapy)	Operation (BMI at total** FU)
1	M	15.3	38.0	34.6	33.9	27.6	82.1	104	104	-	Mammoplasty; revision mammoplasty
2	M	18.5	48.6	47.8	49.0	34.8	58.7	119	119	-	-
3	F	17.9	41.6	37.7	32.9	30.2	68.6	77	77	-	Tonsillectomy
4	M	16.9	46.2	45.1	42.4	45.3	6.8	59	59	-	-
5	F	16.9	39.6	38.7	36.2	46.2	-42.7	41	85	Referred shoulder pain (band removal); weight regain (BPD); intestinal inflammation (hospitalization); incisional hernia (correction)	BPD (22.9)
6	M	14.9	37.0	33.1	31.3	26.1	91.7	71	71	-	Mammoplasty; ptosis correction
7	F	16.2	44.7	40.3	NA	26.6	92.3	63	63	-	Mammoplasty and lower body lift (complicated by hematoma)
8	F	16.7	43.0	34.4	NA	30.5	70.4	55	73	Persistent dyspnoea (band removal)	Band removal (34.0)
9	F	16.7	39.9	NA	NA	34.1	41.2	44	73	Obstruction (desufflation / re-insufflation); weight regain (RYGB); internal hernia after RYGB (repair and re-repair)	RYGB (25.0)
10	F	14.7	51.0	NA	NA	59.6	-26.7	64	64	Slippage (desufflation / re-insufflation)	Band removal (59.6)

Table 3.1 | *Baseline characteristics, weight loss, adverse events and (re)operations*

*OR = operation; 6M = 6 months; 12M = 12 months; %EBMIL = percentage excess BMI loss; LAGB = laparoscopic gastric banding; BPD = biliopancreatic diversion; RYGB = Roux-en-Y gastric bypass; NA = not available. *End of follow-up with in situ gastric band. **End of follow-up after reoperation (when applicable).*

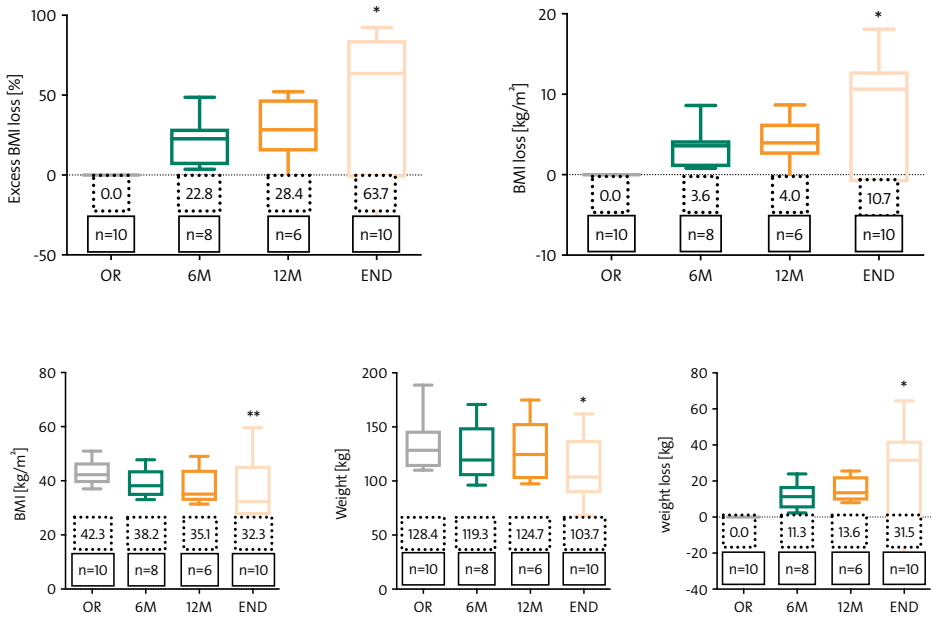

Figure 3.1 | *Weight loss graphs expressing excess BMI loss, BMI loss, BMI, weight and weight loss in the first year and at the end of follow-up with LAGB in situ.*
*True median values are in the dotted boxes. OR = time of procedure. 6M = 6 months follow-up. 12M = 12 months follow-up. END = last visit with gastric band in situ * $p < 0.05$ * * $p < 0.01$ compared to OR.*

cluded: mammoplasty in 2 males and 1 female (combined with lower body lift) and an incisional hernia after BPD. One male patient is currently consulting a plastic surgeon for mammoplasty and lower body lift.

Comorbidity

Existing preoperative comorbidity was mostly limited to musculoskeletal complaints (of the back and lower extremities) and asthma. Table 3.2 demonstrates the diagnosed comorbidities and outcome at the end of follow-up. Diabetes and dyslipidemia did not occur while hypertension in two subjects resolved with weight loss.

Questionnaires

Three patients were not willing to visit our clinic for follow-up in the last year and were therefore unable to complete any questionnaires. The results of the remaining 7 patients and the baseline results are presented below.

	Pre-operative			End of follow-up			
	+	-	NR	Resolved	Improved	Unchanged	NR
Hypertension	2	8	0	2	-	-	-
Diabetes	0	10	0	-	-	-	-
Dyslipidemia	0	7	3	-	-	-	-
Musculoskeletal complaints	10	0	0	4	1	2	3
Asthma / dyspnea	7	2	1	1	4	-	2

Table 3.2 | *Comorbidity. NR = not reported. Hypertension: diastolic > 140 mm Hg or systolic > 90 mm Hg. Diabetes: HbA1C > 6.25 or > 44 mmol/mol Hb, fasted glucose > 7.0 mmol/l. Dyslipidemia: total cholesterol > 6.4 mmol/l, HDL cholesterol < 0.9 mmol/l, LDL cholesterol > 4.4 mmol/l or triglycerides > 1.94 mmol/l.*

Reported Health Status

Figure 3.2 represents the scores on the subscales of the SF-36 health status questionnaire with Dutch population references. The median score is within the mean ± 1 SD reference for all factors, but two subjects consistently score below the -1 SD reference on 5 or 6 subscales. Both low-scorers are male, still have a gastric band, and lost 59 and 92% excess BMI, respectively. All but 1 patient, including these 2, reported that they would have opted for LAGB at this young age again.

Eating Behavior

Preoperative EDE-Q was available in 8 and NVE in 9 patients. Six patients had completed the questionnaires both before and after the procedure. There were no statistically significant differences in any of the subscales (Figure 3.3). Patients score particularly high on the weight and shape concern scales of the EDE-Q when compared to norm scores for a normal-weight population. Although weight concern on the EDE-Q shows the most substantial decrease, the change did not reach statistical significance ($p = 0.07$).

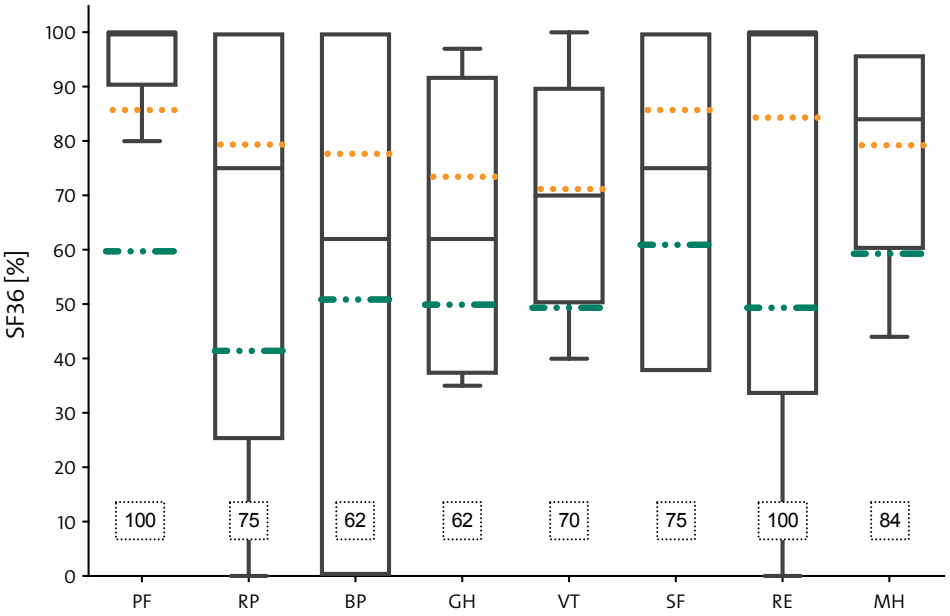

Figure 3.2 | *Subscale scores on the SF- 36 quality of life questionnaire at the end of follow-up. Median values are presented in the dotted boxes. The orange dotted bars indicate the Dutch population mean. The green dashed bars indicate one standard deviation below mean. PF = Physical functioning; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role emotional; MH = mental health.*

Personality Traits

Three patients completed the NPV at preoperative screening, while 5 younger patients completed the NPV-J. Preoperative scores for neuroticism, social anxiety, and dominance are therefore available for 8 patients. There was no consistency in low or high scoring for neuroticism or social anxiety, nor was there any consistent change (Figure 3.4 a, b). There was however a change for dominance. Preoperatively, 5/7 subjects scored below average, but all subjects had increased scores at the latest follow-up (2/7 average, 5 above, Figure 3.4 c, BL vs. END $p < 0.05$).

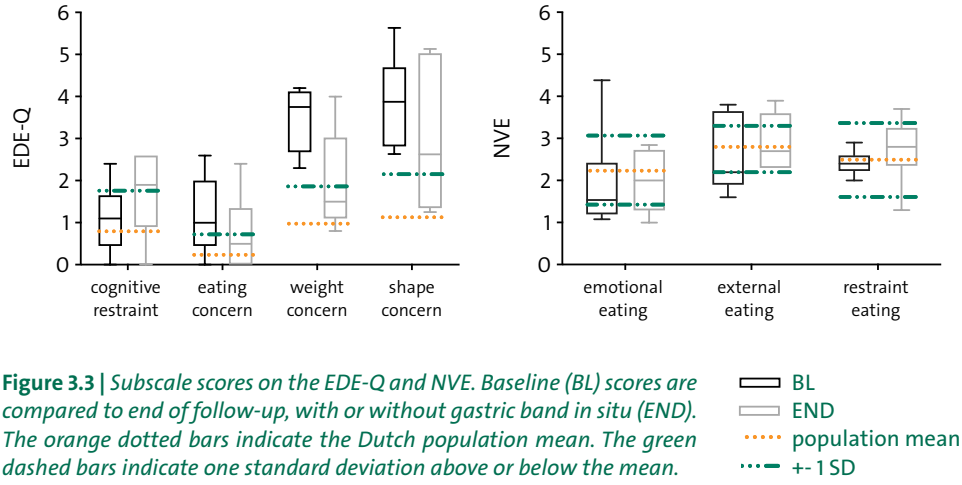

Figure 3.3 | *Subscale scores on the EDE-Q and NVE. Baseline (BL) scores are compared to end of follow-up, with or without gastric band in situ (END). The orange dotted bars indicate the Dutch population mean. The green dashed bars indicate one standard deviation above or below the mean.*

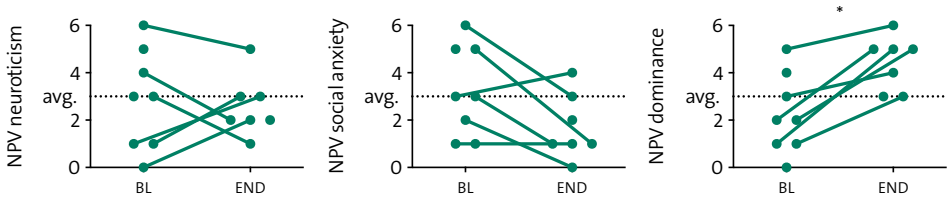

Figure 3.4 | *Neuroticism, social anxiety and dominance as scored on the NPV and/or NPV-J before surgery (BL) and at the last follow-up visit, with or without gastric band in situ (END). * BL versus END p<0.05.*

DISCUSSION

LAGB led to successful weight loss (>50% excess weight reduction) in 6 out of 10 patients after a median follow-up of 64 months. The length of follow-up in this study was crucial. Most weight loss was not achieved in the first postoperative year but after that. The first band desufflation was done after 2 years, while after 3.5 years the first gastric band was removed. So, had we studied this group after 2 or 3 years, the results would have been very different. Comorbidity before surgery, which was mostly limited to musculoskeletal and asthmatic complaints, showed resolution or improvement in most patients. There was 1 patient with adequate weight loss in whom the band was removed because of adverse effects. This patient remained at a stable – healthy – weight while studies in adults have shown that band removal is strongly associated with rapid weight regain (18). We hypothesize that in this young individual restrictive bariatric surgery may have led to a permanently adjusted lifestyle and behavior towards food, since it is generally accepted that behavior changes are easier at younger age. Two patients in whom inadequate weight loss was achieved with LAGB successfully lost weight after conversion to a malabsorptive procedure. These procedures were however associated with more severe adverse effects, including two corrective procedures for internal hernia, a serious complication known to be associated with RYGB (19).

The reported physical and mental health status after LAGB is well within the Dutch population norms in 5 out of 7 patients. The 2 patients who perceived low mental and physical health status had successful weight loss and reported to be satisfied with their gastric band. However, one is struggling with body image and applied for corrective surgery, and the other was recently released from prison, which probably influences wellbeing more than the results of gastric banding.

Since bariatric surgery in adolescents was very exceptional at that time, and still is in the Netherlands, only a small group of patients could be included. There were no significant changes in eating behavior after LAGB. However, even in this small group, weight concern showed a decreasing trend. An interesting observation is the significant shift from a low dominant personality score to a higher score for all patients. The items involved in dominance relate to taking initiative, leadership, and confidence in a group. A low score on hostility, a scale reflecting criticism to others and distrust, seemed to be in line. However, low scores were also observed for self-esteem. Overall,

the scores on the NPV reflected gained trust in positioning oneself towards others and feeling confident in contact with others, while still having a relatively low self-image. Whether this change was attributable to weight loss, aging or both cannot be concluded without a control group.

Despite well-organized preoperative evaluation and postoperative follow-up, there is missing data due to poor reporting and 30% loss to follow-up in the past year. Still, follow-up in this study is longer than the vast majority of the available literature. A recent review found only one long-term retrospective LAGB study with more than 36 months follow-up in adolescents (6). Meta-analysis of all eligible studies showed a BMI reduction of 11.6 kg/m² while the long-term study by Silberhumer et al. (20) showed BMI loss of 18.1 kg/m² (93% excess weight loss) after 60 months follow-up. They showed that most of the weight loss occurred in the first 3 years while most complications occurred afterwards, which is in line with what was found in the present study.

Gastric banding is losing popularity in adults compared to sleeve gastrectomy and RYGB as the bariatric procedure of choice, but it carries definite advantages. It is the procedure with the lowest operative risk, and it is effective in the majority of patients. It does not alter gastrointestinal anatomy and is completely reversible. When weight loss is unsuccessful, a malabsorptive procedure as a second step seems a feasible and effective option for those who failed.

Conclusion

LAGB in morbidly obese adolescents had a primary failure rate of 40% after long-term follow-up, but was a successful therapy in the other 60% without major adverse events. Conversion to malabsorptive procedures after unsuccessful weight loss was effective but associated with complications related to their invasiveness. We strongly encourage studies to continue follow-up for at least 5 years and to look at both weight loss and complications with the gastric band in situ and after conversion to more invasive procedures. Larger prospective studies should provide more insight in changed eating behavior and personality.

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Bariatric Surgery in Adolescents: a Prospective Randomized Controlled Trial Comparing Laparoscopic Gastric Banding to Combined Lifestyle Interventions in Adolescents with Severe Obesity

(BASIC trial)

ABSTRACT

BACKGROUND

Obesity in children and adolescents is an increasing problem associated with multiple comorbidities including metabolic and endocrine changes, cardiovascular abnormalities, and impaired quality of life. Combined lifestyle interventions are the current standard treatment for severe obesity in children. However, the medium- and long-term results of these interventions are relatively poor. Bariatric surgery shows substantial weight loss and health improvement in adults and retrospective studies in adolescents show similar outcomes. However, well-designed prospective studies in this young age group are rare. Our objectives are to determine whether combining surgery with lifestyle interventions in severely obese adolescents leads to a significant additional weight reduction compared to lifestyle interventions solely, and to assess its effect on obesity-associated comorbidities in a prospective randomized controlled setting.

METHODS

Patients aged 14–16 years with sex- and age-adjusted BMI > 40 kg/m² (or > 35 kg/m² with comorbidity) and failure to achieve weight

reduction > 5% during at least one year of combined lifestyle interventions are included in this trial. Randomization determines whether laparoscopic adjustable gastric banding will be added to combined lifestyle intervention throughout the trial period. Sixty children will be included in this trial. Follow-up visits are planned at 6 months, 1, 2 and 3 years. Primary endpoints are percentage of total weight loss, and change of BMI. Secondary endpoints include body composition, pubertal development, metabolic and endocrine changes, inflammatory status, cardiovascular abnormalities, non-alcoholic steatohepatitis, quality of life and changes in behaviour.

DISCUSSION

This randomized controlled trial is designed to provide important information about the safety and efficacy of laparoscopic adjustable gastric banding treatment in severely obese adolescents with unsuccessful combined lifestyle interventions. The reversibility of this surgical procedure forms a strong argument to decide for gastric banding over other surgical procedures, since bariatric surgery in adolescents is still in its infancy.

BACKGROUND

Overweight and obesity in children has become a global health problem during the past decades. It has already been designated as 'one of the most serious public health challenges of the 21st century' by the World Health Organization (1). Obesity during childhood can have serious consequences for several organ systems including the cardiovascular and the endocrine, and can result in psychosocial comorbidity (2, 3). Furthermore, children with overweight and obesity are prone to become obese adults, with an on-going risk of comorbidities (4–6). If obesity is more severe, or shows a greater variability or rapid increase, adolescents are less likely to grow out of their obesity (4, 7).

In accordance with treatment in adults, there are various treatment methods for overweight and obesity in children. Several interventions have been studied in childhood populations (8–11). Lifestyle interventions are often based on physical activity, dietary and/or behavioural interventions. Combination of these non-pharmacological lifestyle components can result in a decrease in body mass index (BMI) up to 12 months after treatment, but effect sizes remain small (8). Evidence for long-term weight control following these lifestyle interventions in children is scarce, but it should be noted that in adults the majority of these interventions have been proven to be ineffective in long-term weight control (12, 13). Pharmacological treatment can enhance weight loss when prescribed as additional therapy next to lifestyle interventions (8). Both orlistat and sibutramine seem to be effective in adolescents, but again the effects remain small and long-term data is limited (14–18).

Since the risk of associated comorbidity increases with an increasing BMI, the need for an effective and long-term solution to lose weight is even more urgent for children and adolescents with severe obesity (19, 20). In the adult population, bariatric surgery is widely accepted as treatment for severe obesity. Bariatric surgery enables patients to lose more weight compared to non-surgical interventions, regardless of the type of surgery (21). In addition, the effect of bariatric surgery has been proven to persist over many years, leading to reduction in mortality and obesity-associated comorbidity in the long-term (21–23). Because of ethical considerations and the potential for serious complications, bariatric surgery is not generally accepted (yet) as a last-resort treatment option in therapy-resistant severely obese children. In order to substantiate the additional value of bariatric surgery compared to treatment with lifestyle interventions alone, more evidence on safety and effectiveness of childhood bariatric surgery is required. Few prospective cohort studies on childhood bariatric surgery have been published. The majority of these studies address one of the three common bariatric procedures:

laparoscopic adjustable banding (LAGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic Roux-en-Y gastric bypass (LRYGB) (24, 25). In general, these cohort studies suggest effective weight loss up to 36 months (–10 to –15 BMI points depending on the procedure) (26). However, only one randomized controlled trial has been carried out to compare bariatric surgery with conventional treatment in adolescents, resulting in –12.7 versus –1.3 BMI points after 2 years for intervention and control group respectively (27). The present study differs from this previous study, as we include only patients who underwent lifestyle interventions in a multidisciplinary setting before for more than 1 year and nevertheless failed to lose weight (10, 11).

Despite the lack of the highest quality evidence that bariatric surgery in adolescents is safe and can be successfully done, this treatment has been popularised in certain countries to treat adolescents with severe obesity. In most countries in Europe, they are more reluctant to do an operation for severe obesity, or bariatric surgery in youngsters is not performed at all.

STUDY OBJECTIVES

Combined Lifestyle Interventions (CLI) are the current standard to obtain weight reduction in severely obese children and adolescents (10, 28, 29). The main aim of the 'Bariatric Surgery in Children' (BASIC) randomized controlled trial is to investigate whether last-resort LAGB treatment in children and adolescents is safe and effective in terms of (excess) weight loss and loss of excess BMI. Secondary objectives in this trial focus on obesity associated comorbidity and include assessment of body composition, pubertal development, metabolic and endocrine changes, inflammatory status, cardiovascular abnormalities, non-alcoholic fatty liver disease, quality of life, general and food-specific cognitive processes, changes in behaviour and effects on sleep architecture.

	Boys		Girls	
Age [years]	BMI 35 [kg/m²]	BMI 40 [kg/m²]	BMI 35 [kg/m²]	BMI 40 [kg/m²]
14	32.9	38.4	33.3	39.4
15	33.7	39.1	33.9	39.7
16	34.2	39.5	34.3	39.9

Table 4.1 | *Age- and sex-adjusted BMI cut-off points for severely obesity in the Dutch population (29)*

METHODS

Study design

We will perform a prospective superiority trial by randomizing severely obese children and adolescents in a 1:1 ratio to receive LAGB on top of the CLI versus CLI treatment alone. The study protocol meets the criteria of the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) Guidelines (online additional file 1: Appendix 1) (30). The trial will be carried out at the Maastricht University Medical Centre in the Netherlands. Outcomes will be measured at 6, 12, 24 and 36 months from randomisation and will be evaluated after 12 and 36 months.

Study population

Inclusion criteria

The study population includes severely obese children who underwent long-term multidisciplinary lifestyle interventions without the intended effect. All children referred to our clinic for enrolment in the trial are screened for the following inclusion criteria: age 14, 15 or 16 years old; age- and sex-adjusted BMI > 40 kg/m² or > 35 kg/m² with obesity associated comorbidity (Table 4.1) (29, 31); and participation in at least one multidisciplinary organized paediatric weight reduction program (as combined lifestyle interventions, CLI) for a minimum period of 12 months, without accomplishing the intended effect of 5% weight loss or more. The CLI should be coordinated and monitored by a paediatrician and include at least regular dietary advice and monitoring from a certified dietician, regular exercise training and behavioural therapy from a trained psychosocial worker.

Obesity-associated comorbidity in this young population has been defined as one or more of the following: a) glucose intolerance (fasting glucose > 6.1 mmol/L); type 2 diabetes mellitus (T2DM; fasting glucose > 7.0 mmol/L and/or oral medication on prescription for known T2DM); b) hypertension (blood pressure > 140 mmHg systolic and/or > 90 mmHg diastolic, and/or oral medication on prescription for known hypertension); c) dyslipidaemia (total cholesterol > 6.5 mmol/l, low-density lipoprotein cholesterol > 4.4 mmol/l, high-density lipoprotein cholesterol < 0.9 mmol/l, triglycerides > 1.94mmol/l and/or oral medication on prescription for known dyslipidaemia); d) obstructive sleep apnoea (OSA; apnoea-hypopnoea index > 5/h, or continuous positive airway pressure treatment for known OSA); e) non-alcoholic steatohepatitis (serum alanine aminotransferase > 45 U/L for males and > 35 U/L for females, or steatohepatitis proven by biopsy); f) depressive disorder (as diagnosed according to the DSM-IV or DSM-V) (32);

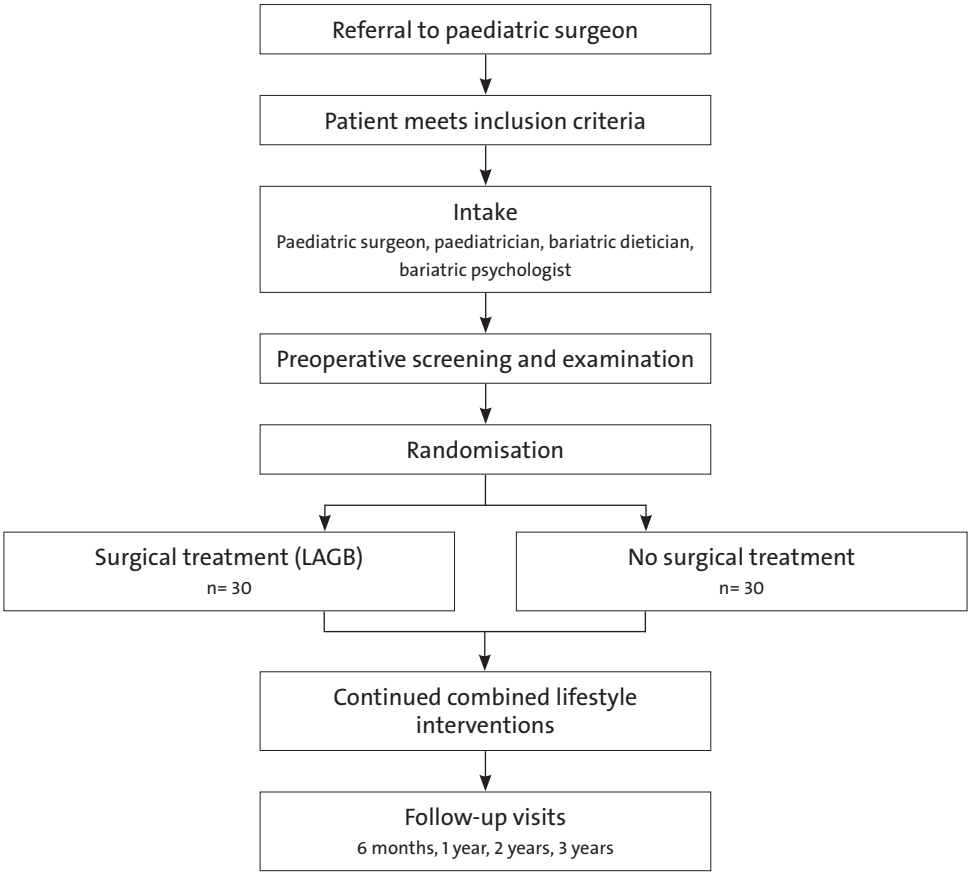

Figure 4.1 | *Flowchart of the BASIC trial study design*

g) arthropathy; acanthosis nigricans; and/or idiopathic intracranial hypertension.

Only the comorbidities diagnosed and reported by the treating paediatrician and/or general practitioner of the patient are noted during assessment of inclusion criteria. The participation in one or more multidisciplinary weight reduction programs for a minimum period of 12 months needs to be confirmed by the referring physician.

In addition to the obesity-related inclusion criteria, patients will need to demonstrate an adequate level of decisional capacity, a sufficient level of Dutch language comprehension and awareness of the randomization process with all its consequences; this will be assessed by an independent specialised youth psychologist during an intake session.

Exclusion criteria

The exclusion criteria for this trial are a) eating disorders ('binge eating', defined as compulsive overeating or consuming abnormal amounts of food while feeling unable to stop and at loss of control' and 'grazing', defined as repetitive periods of eating small amounts of food in an unplanned manner, at least twice daily; b) unrealistic expectations of weight loss; and inadequate social support of the family or caregivers, all to be assessed by the independent specialised youth psychologist and dietician. Dutch translations of validated questionnaires will be used for the assessment of the specific eating disorder exclusion criteria (i.e. the Eating Disorders Examination Questionnaire for Children, chEDE-Q); c) skeletal or developmental immaturity (premenarchal girls, boys with bone age younger than 15 years on X-ray of the hand); d) severe cardiorespiratory impairment (ASA class 3 or more); and e) syndromic disorders causing obesity (e.g. Prader-Willi syndrome). Other exclusion criteria are physical disorders with highly possible influence on weight, such as untreated hypothyroidism or prolactinoma; and unwillingness to adhere to the follow-up program.

Study outline

A paediatrician or general practitioner can refer adolescents to the BASIC trial research team at Maastricht University Medical Centre. The referring physician will report general background of the patient, physical status and previous attempts to reduce weight including lifestyle interventions (among others). If the inclusion criteria on age, BMI and lifestyle interventions are met, the patient and his/her parents will be contacted and invited for an extensive intake at our medical centre. The surgeon, paediatrician, bariatric dietician, paediatric psychologist and clinical investigator (MD) from the BASIC trial research group will carry out the intake session subsequently (Figure 4.1).

During the intake session, the patient and his/her parents or legal guardians will be extensively informed about the various aspects of the trial. A routine physical examination will be carried out to make sure all the inclusion criteria are met. Boys will undergo assessment of their bone age with an X-ray of their left hand; an experienced paediatric radiologist will assess the exact bone age. The bariatric dietician and the paediatrician will assess the quality of the attempts to lose weight and acquire possible contra-indications for enrolment in the trial. The patient will be asked about his or her motivation to enter the trial and the expectations of the surgical procedure and its consequences. The motivation, basic understanding of the possible operation and the expectations will be written down by the patient to verify if he or she has understood which decision is to be made. If patients continue to have too optimistic expectations about surgery, or do not understand the implications and consequences

of the operation, they will not be considered as suitable candidates to participate in the trial. The expert bariatric psychologist will advise both the patient and the parents. Afterwards, the patient will be discussed in a team meeting of paediatric and bariatric surgeons, bariatric dietician, paediatrician and paediatric psychologist. If one or more team members object to inclusion of patient, the patient will not be included in the trial and will be referred back to the referring paediatrician or general practitioner. If the patient is considered suitable to participate in the trial, the investigator will obtain written consent from the patient and both parents / legal guardians for trial participation. The patient will then be admitted to the Maastricht University Medical Centre for extensive physical screening. When a patient shows signs or symptoms of syndromic abnormalities or other disorders being a possible cause of obesity (e.g. hypothyroidism), further investigations will be carried out and treatment (other than being bariatric surgery) will be provided by the referring physician. If the physical screening shows no significant abnormalities possibly causing obesity, the patient can proceed to randomization (Table 4.2).

The investigator will randomise all patients approved for inclusion in either the 'surgery and lifestyle group' (intervention group) or the 'lifestyle control group' (control group) at a 1:1 ratio by block randomization. A statistician affiliated with our medical centre will create random blocks using a digital randomization program; the blocks can consist of two, four or six patients. This resulted in 60 sequentially numbered, opaque and sealed envelopes only accessible for principal investigator and paediatric surgeon LvH and for investigator YR. The investigator, bariatric surgeon, paediatric surgeon, patient and his/her parents will not be blinded for randomisation outcome, but will be blinded for the randomisation list. Other care providers from the Maastricht University Medical Centre will be blinded, as will be the data analysts and outcome assessors other than the investigators. Referring paediatricians and general practitioners will not be blinded, to assure adequate care and awareness for potential complications throughout follow-up.

The patients in the intervention group will be readmitted to the surgical centre within 6 weeks after randomisation for routine preoperative evaluation. The dedicated bariatric dietician from the research team will visit the patient and accompanying parents on the ward and provides them with extensive dietary advice and guidelines for the home-based setting. A booklet with summary of the advice will be handed over in duplicate, to make sure the dietician in the CLI treatment team at centre of referral will be provided with the same information. The bariatric surgeon and paediatric surgeon will visit the patient and parents that same day, to reconfirm informed consent for surgery and provide all the information about the surgical procedure, postoperative phase and follow-up. The next day the patient will be operated on

	Study Period						
	Enrolment	Allocation	Post-allocation*				Close-out
Timepoint	-t1	0	t6	t12	t24	t36	tx
Enrolment							
Eligibility screen	•						
Informed consent	•						
Allocation		•					
Interventions							
CLI		•	◄	———	———	———	►
LAGB + CLI		•	◄	———	———	———	►
Assessments							
Body composition	•		•	•	•	•	
Metabolic status	•		•	•	•	•	
Endocrine status	•		•	•	•	•	
Inflammatory status	•		•	•	•	•	
Non-alcoholic fatty liver disease	•			•	•	•	
Cardiac pathology	•			•	•	•	
Sleep abnormalities	•			•	•	•	
Microvascular status	•			•	•	•	
Macrovascular status	•			•	•	•	
Behavioural changes	•		•	•	•	•	
Health-related Quality of Life	•		•	•	•	•	
Physical activity	•		•	•	•	•	

Table 4.2 | *Schedule of enrolment, interventions and assessments of the BASIC trial. CLI combined lifestyle interventions, LAGB Laparoscopic adjustable gastric banding. *Time points noted in months.*

under general anaesthesia and receives a LAGB (LAP-BAND AP® Adjustable Gastric Banding System, Allergan Inc., Dublin, Republic of Ireland) using the pars flaccida technique (33). The expected postoperative hospital stay is one or two days. After 6 weeks, the gastric band can be insufflated gradually if necessary. Adjustments to the volume of the gastric band will be performed at our medical centre and include X-ray control to evaluate the effect of any adjustment, all adjustments will be registered in a standardized file. Afterwards the patient receives yearly routine surgical follow-up, or more often if medically necessary.

All patients participating in the trial (both intervention group and control group) will receive lifestyle interventions and follow-up throughout the entire trial period. All patients will return to the paediatrician, dietician and psychologist of the referring obesity clinic for continuation of the lifestyle program. The multidisciplinary follow-up of the previous life style interventions will be continued in both groups after randomisation to guarantee the best achievable weight loss in both study groups. The investigator will monitor the post-inclusion care by a telephone follow-up call once every 3 months. All patients will be subjected to an extensive clinical review at the surgical centre at 6 months, 12 months, 2 years and 3 years after inclusion. Adherence to the routine follow-up visits will be registered.

To date, bariatric surgery in children and adolescents is prohibited in The Netherlands for all clinical settings except for this trial. Patients from the control group who turn 18 years during the trial period are offered to crossover to the intervention group and receive surgical treatment. If the patient decides for any other type of weight loss surgery after turning 18, this event will be registered yet the patient will still be invited for follow-up visits and be part in the 3-year follow-up analyses. If this trial will provide sufficient data proving that surgical treatment in adolescents is safe and effective, the Dutch Health Care Inspectorate will evaluate and decide whether the remaining patients from the control group can be offered to crossover to the intervention group.

Patients who withdraw from the trial prematurely will receive their regular follow-up from the referring paediatrician. If patients have been operated upon, they will receive their regular surgical follow-up and treatment, but additional trial related investigations will be discontinued.

Outcomes

Primary outcome measures

These are defined as percentage total weight loss (%TWL) and change in BMI. Height will be noted to the nearest 0.1 cm and body weight to the nearest 0.1 kg, measured with a stadiometer and digital scale respectively with children dressed in underwear. Self-reported weight data will never be used. BMI will be calculated by dividing weight in kilograms by height in meters squared; excess BMI and excess weight will be calculated according to the cut-off points as shown in Table 4.1.

Secondary outcome measures

In addition to height and weight, other anthropometric measurements will be used to assess body composition, including neck, waist and hip circumferences, and skinfold thickness at standardised anatomical points. Dual energy X-ray absorptiometry (DXA) will be used to assess bone density and calculate fat and lean tissue mass. More specific measurement of weight distribution over the different body compartments will be carried out by total body water (TBW) measurement using deuterium dilution (34).

Metabolic and endocrine changes in body homeostasis will be assessed by biochemical analysis of glucose metabolism parameters (both fasting and during oral glucose tolerance test), lipid metabolism parameters (cholesterol, free fatty acids, and triglycerides), thyroid function parameters (thyroid stimulating hormone, free T4, parathyroid hormone) and gonadotropins. Decreased insulin sensitivity (insulin resistance) will be measured using the homeostatic model assessment of insulin resistance (HOMA-IR), while glucose intolerance and diabetes will be defined according to the American Diabetes Association (35–37). Daytime blood pressure will be measured while resting during a period of 60 to 90 min (intervals of 3 min between measurements) using the Mobil-O-Graph ® NG (I.E.M. GmbH, Stolberg, Germany). Hypertension and prehypertension will be defined according to the National High Blood Pressure Education Program update on American guidelines (38). Inflammatory status will be assessed by biochemical analysis of inflammatory variables.

Liver functioning and potential non-alcoholic hepatitis steatosis will be monitored by testing biochemical liver function variables. Furthermore, a specialised paediatric radiologist will carry out a standardised ultrasound investigation of the liver to screen patients for structural liver abnormalities, monitor liver dimensions and obtain a rough estimate of hepatic steatosis.

Cardiac functioning will be investigated by a specialised paediatric cardiologist, who will perform Doppler echocardiography in each patient yearly, assessing the

cardiac dimensions and potential left ventricle hypertrophy. Macrovascular changes will be monitored throughout the trial by measurement of the carotid intima-media thickness, carotid-femoral pulse wave velocity, pulse waveform analysis and flow mediated dilation of the brachial artery (39–41). Microvascular changes will be measured by testing nailfold capillary density and post occlusive nailfold capillary recruitment (42). Vasomotion of the microcirculation in the skin will be measured at wrist level during the oral glucose tolerance test using laser Doppler flowmetry (43, 44).

Quality and architecture of sleep and potential obstructive sleep apnoea will be analysed objectively with an annual polysomnography. Patients will be asked to carry an accelerometer at standardised time points during follow-up. The meter will then be carried for 7 days while performing regular activities. A diary will be kept during these 7 days to gain more insight in the activities. At the same standardised time points patients will be asked to fill out a Baecke questionnaire (adapted for children) evaluating work activity, sports activity and non-sports leisure activity (45).

Eating behaviour and response to food stimuli will be assessed with Dutch translations of validated self-report questionnaires, including the Eating Disorders Examination Questionnaire for Children (chEDE-Q), the Three Factor Eating Questionnaire (TFEQ) and the Power of Food Scale (PFS) (46–48). A computerized version of the Iowa Gambling Task (IGT) will be used to investigate decision making and reward dominance of the study participants (49, 50). The Stop Signal Test (SST) will be used to measure response inhibition and monitor potential changes throughout the study (51). In order to study the rewarding value of food items, the patients will play a Wanting and Liking Test (WLT) before and after a standardised meal (52).

Psychosocial status and functioning will be assessed both at the beginning and throughout the trial. Health-related quality of life (HRQOL) will be monitored with use of the Dutch translation of the Pediatric Quality of Life Inventory (PedsQL) for children aged 13 to 18 years (53). In addition, the Beck Depression Inventory (BDI)-II will be used to gain more insights in psychosocial functioning (54).

All outcome variables will be measured at baseline, 12 months, 24 months and 36 months. At 6 months, all examinations will be carried out except for DXA, liver and cardiac ultrasound, microvascular and macrovascular changes and the polysomnography.

Sample size

The total number of needed study participants was calculated for the primary outcome measure weight loss and is based on the following assumptions: (1) the expected weight loss after 1 and 3 years in the surgery group is 25%; (2) the expected weight change in the control group is 0%, as the patients in the control group have previously

been unsuccessfully treated with combined lifestyle interventions; (3) the expected standard deviation is 10% for both groups (55). To assess a difference in weight loss of 10% or more (7% weight loss is considered to be relevant as it results in a significant improvement in risk and comorbidity in severely obese adolescents), 44 patients have to be included (α= 0.05, ß= 0.10) (56). Based on previous studies in adults at our institution, we assume that approximately 20% of the patients will not finish the one-year follow-up period, 60 patients need to be included into the study to preserve results on 44 patients treated per protocol. The number of patients necessary to show significant relative excess weight loss or loss of relative excess BMI is smaller. The sample size needed to detect significant and relevant weight loss after surgery compared to conservative treatment will also be sufficient to assess significant differences in insulin resistance and hypertension between both groups. The expected resolution of both insulin resistance or diabetes, and hypertension after surgery is 70–90%, while no effect of continuing life style interventions can be expected (55, 57). For most of the other variables the currently available information about the expected outcome is not sufficient for a reliable power analysis.

Data collection and management

Standardized case report forms will be used for source data during the trial and stored by the investigator in a locked, fireproof place. To ensure privacy of the participants, identifying data will be stored in coded form secured by a password only known to the investigator and principal investigator. Tissue and plasma samples will be stored in coded form and stored in a locked freezer at the surgical laboratory of the principal investigator. Data and human material will be kept for 15 years. Statistical analyses are done by the professional statistician participating in the research staff of the study (online additional file 2: Appendix 2).

In order to ensure data quality, both the cardiac and liver ultrasound will be carried out by clinical experts and measurements are repeated at least twice per participant per examination. The DXA outcome variables will be evaluated by two specialised nuclear physicians. Anthropometric measurements and microvascular and macrovascular investigations will be performed by a trained laboratory technician; duplicate measurements will be carried out for all of these specific outcomes.

The results of the study will be presented at scientific meetings and published in peer-reviewed medical journals.

Safety

Serious adverse events and adverse events will be registered in accordance to the standards of Good Clinical Practice. The Dutch Health Care Inspectorate will supervise this clinical trial independently and performs unannounced audits. All early and late operative complications such as wound site infections, slippage of the gastric band, and pouch dilatation of the created gastric pouch will be monitored throughout the entire duration of the trial according to the Clavien-Dindo scoring system (58). Puberty development will be monitored with growth (body height) and plasma levels of gonadotropins and sex hormones. Nutritional status will be assessed to prevent malnutrition.

The study will be terminated prematurely in case of serious and unexpected complications of surgery, if the complication rate of surgery exceeds the 95% confidence interval of the 10% complication rate considered as normal and in case of serious adverse events that are directly related to the diagnostic procedures performed in this study.

Monitoring

To monitor the safety of all patients included in the trial, a Data Safety Monitoring Board (DSMB) will be installed. The board will consist of three independent physicians from the departments of General Surgery and Paediatrics of the Maastricht University Medical Centre. The progress of the trial will be reported to the DSMB after every tenth inclusion in the trial. The report will contain data on all complications of surgery, all adverse events, major protocol deviations and other relevant information per coded participant. The opinion of the DSMB and consequent binding (dis)approval of continuation of the trial will be written down and stored in the trial master file. The medical ethics committee of Maastricht University Medical Centre will be informed about the DSMB opinions.

DISCUSSION

The BASIC trial is designed to provide high-quality data on the safety and efficacy of LAGB treatment in severely obese children and adolescents. Lack of available long-term data on safety and efficacy of bariatric surgery in youngsters advocates an extremely cautious approach and intensive monitoring of growth and development in these specific patients. Nevertheless, severe obesity has already proven to impair children and adolescents in their pubertal and psychosocial development and significantly increases risks for development of cardiovascular diseases, amongst others (2–6). The BASIC trial will provide tertiary and multidisciplinary care for its participants: comprehensive health examinations will be carried out throughout the trial and results will be discussed in a multidisciplinary setting to guarantee optimal care for this vulnerable population. This is the first randomized controlled trial investigating bariatric surgery as a complementary treatment in adolescents with failed combined lifestyle interventions. Outcome measurement will focus primarily on percentages of total weight loss and excess weight loss, yet a comprehensive set of secondary outcome measures will be provided as well.

A potential limitation of this study includes the choice of LAGB treatment over other bariatric procedures as investigational intervention. Laparoscopic adjustable gastric banding is a restrictive bariatric procedure that can be reversed easily and enables weight loss without altering absorptive processes. The reversibility of the LAGB procedure formed an important argument in this study design of this experimental trial, since the study population is very young and patients might want to make use of possible new and innovative treatment options in the future. Other bariatric pro-

cedures have proven to be more effective in terms of excess weight loss and improvement of comorbidity in adults, though these results do not necessarily apply to children and adolescents in the same extent (21, 25).

Secondly, this study may be at risk for relative high loss to follow-up rates throughout the study period. Because of the comprehensive attempts to lose weight (without intended effect) prior to enrolment in this study, patients may have developed a certain attitude towards healthcare systems and providers negatively affecting their compliance and their stamina. Allocation to the control group might amplify these developments, resulting in high risks for getting loss to follow-up. The coordinating investigator of the BASIC trial will be aware of these risks and attempt to keep the patients involved with their own health status and potential beneficial treatment methods. Patients and their parents will be informed of the results of their annual comprehensive medical examination and will be involved in the possible adjustments that have to be made to the combined lifestyle interventions and/or gastric band care if applicable.

In summary, this randomized controlled trial will provide important information on the safety and efficacy of LAGB surgery in severely obese adolescents with unsuccessful CLI. The unique control group will provide a necessary framework of data regarding physiological changes throughout adolescence and pathophysiological effects of persistent childhood severe obesity. The results of this study may steer the international opinion regarding treatment options of severely obese adolescents who still have most of their lives ahead of them.

APPENDICES

Appendix 01

SPIRIT Checklist available with the online publication

Appendix 02

Statistical analysis plan for outcome measurements

Descriptive statistics

Numerical data will be tested for normality with the Kolmogorov-Smirnov statistics and will be presented as mean ± standard deviation if there is a normal distribution, otherwise as median (range). Categorical data will be presented as number (percentage).

Longitudinal treatment effect

Linear and logistic mixed models will be used to assess the longitudinal treatment effect for numerical and categorical outcome variables, respectively. This analysis method accounts for the correlation between repeated measures, uses all available data, and uses a likelihood approach for missing outcome data, which are assumed to be missing at random (MAR). Group, time and group*time will be included as fixed factors to assess the treatment effect at different time points. Variables related to missing outcome data, based on logistic regression analyses, will be included to the fixed part of the model to ensure MAR. As for the random part, random intercept and/or slope will be considered, where the best option will be selected based on Bayesian Information Criterion (BIC). As sensitivity analysis, baseline characteristics that substantially differ between groups are then also included in the model.

Interim analysis (if applicable)

Not applicable.

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Endoscopic Gastric Volume Reduction with a Novel Articulating Plication Device is Safe and Effective in the Treatment of Obesity

ABSTRACT

BACKGROUND

Endoscopic volume reduction of the stomach may provide a minimally invasive alternative for surgical procedures in the treatment of obesity.

OBJECTIVE

To assess safety and preliminary effectiveness in the first human application of a novel endoscopic stapling technique.

DESIGN AND SETTING

Prospective observational Phase 1 study. Two university hospitals in the Netherlands.

PATIENTS AND INTERVENTION

Patients with a BMI of 40–45 kg/m² or 30–39.9 kg/m² with obesity-related comorbidity. Gastric volume reduction with an endoscopic stapler.

MAIN OUTCOME MEASUREMENTS

Primary outcome measure was the prevalence of serious or non-serious adverse events. Reduction of excess body weight after 12 months was assessed as a secondary outcome measure for effectiveness of the procedure.

RESULTS

Seventeen patients with a median BMI of 40.2 kg/m² (IQR 37.6–42.8) underwent an endoscopic stapling procedure. Median procedure time was 123 (IQR 95–129) minutes. No serious adverse events occurred. Adverse events were gastric pain (n=7, range 1–3 days), sore throat (n=4, 2–3 days), diarrhea (n=4, 2–15 days), nausea (n=3, 2–4 days), constipation (n=4, 3–14 days), and vomiting (n=3, 1–4 days). All adverse events were mild and resolved with conservative treatment within 15 days after surgery. The median percentage excess weight loss in the first year was 34.9% (IQR 17.8–46.6).

CONCLUSIONS

This first human application of this endoscopic stapler demonstrates that the procedure is technically feasible and safe. One hundred and sixty plications were created in 17 patients without significant problems. Weight loss after one year is promising, but long-term follow-up and randomized controlled studies should evaluate whether this procedure is an effective and durable minimally invasive endoscopic treatment for obesity.

INTRODUCTION

Obesity has gradually become pandemic; it now affects an estimated 300 million people worldwide. The incidence has grown remarkably over the last decades: up to 32% of the adult population in the United States (US) and 10–25% in the European Union are obese (1, 2). The World Health Organization (WHO) defines morbid obesity as a body mass index (BMI) of 40 kg/m^2 or higher, which indicates a risk of morbidity and premature death due to excess weight. In the US, 3.7–6.6% of the adult population is morbidly obese (3). Associated morbidity includes hypertension, diabetes mellitus type II (DMII), coronary heart disease, osteoarthritis and cancer. Therefore, morbid obesity also greatly burdens health care systems (4).

Since the number of morbidly obese patients is increasing, more people require treatment. As bariatric surgery is the only long-term effective treatment for morbid obesity, a big demand is being placed on surgical capacity. Underlying mechanisms to achieve weight loss are based on food restriction, malabsorption or a combination of both to create earlier satiety and improve metabolism. The most important result of bariatric surgery is a reduction of comorbidities. Moderate weight loss (5–10% of initial weight) results in health benefits and a reduction of comorbid disorders in obese subjects (5). For the morbidly obese, a weight loss of 15–25% is required to achieve these benefits.

Excess weight loss after both gastric bypass and sleeve gastrectomy is approximately 65–70% and approximately 45–50% after gastric banding (6). However, these surgical procedures are associated with considerable morbidity (7–12). The most common adverse events after laparoscopic Roux-en-Y gastric bypass include wound infection (3.0%), anastomotic leakage (2.1%) and, in the longer term, anastomotic stenosis (4.7%) and internal herniation (1.1%) (12, 13). The mortality rate of gastric bypass surgery varies between 0.2% (laparoscopic) and 0.9% (open) (12, 13). The sleeve gastrectomy is an increasingly popular technique, but it also has a significant leak risk (2.4%) (10). Bariatric surgery is indicated when the expected health gain exceeds the risk of surgery. This implicates that fragile patients with a high risk of complications and patients who do not meet the current criteria for bariatric surgery (i.e. patients that are 'not heavy enough') cannot profit from its advantages.

Endoscopic procedures that are able to cause food restriction and/or malabsorption may provide an attractive, less invasive and possibly less expensive alternative for a broader group of potential beneficiaries. Endoscopic procedures such as the EndoBarrier, TOGA (transoral gastroplasty) and POSE (primary obesity surgery endoluminal) procedure have been described in other studies (14–17). The first procedure targets for

malabsorption and altered gastrointestinal physiology, whereas the latter procedures are restrictive. This study evaluates a new transoral restrictive endoscopic procedure in two academic centers. It presents the feasibility, safety and effectiveness of the Articulating Circular Endoscopic (ACE) stapler for gastric volume reduction in obese patients.

METHODS

Study design

A two-center Phase I prospective observational cohort study was initiated in March 2012. It was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam, The Netherlands and locally approved by the Maastricht University Medical Center board of directors (March 6, 2012, ClinicalTrials.gov: NCT01429194) and a Safety Committee was appointed.

The ACE procedure

During early development of the ACE procedure, both porcine and canine animal models were explored. While human upper gastrointestinal anatomy differs from that of both animals, the canine stomach tissue more closely resembles human tissue. The current design of the ACE stapler went through over 300 successful ex vivo tests with canine stomach tissue to demonstrate full-thickness tissue aspiration (Figure 5.1). The physicians went through two training sessions to adequately guide the steerable stapling device and safely create plications in the intended areas of the stomach on a live canine animal model. They created approximately 60 plications prior to performing the first ACE procedure in humans.

All clinical cases were performed under general anesthesia (propofol and remifentanil) with endotracheal intubation in the operating room. An experienced technical engineer from BaroSense Inc. (San Francisco, California, USA) was on site providing technical assistance. Standard bariatric surgery regime of prophylactic antibiotic therapy (cefazolin and metronidazol) and a double dose of prophylactic low molecular weight heparin were administered preoperatively to all patients, because of stapling in an unsterile environment and the increased risk of thrombosis in morbidly obese patients. Patients were positioned supine with the head tilted backwards as much as safely possible. A bite block was placed to protect the teeth and CO_2 was used to insufflate the stomach.

After endoscopic inspection of the esophagus, stomach and duodenum ruled out

conditions that precluded participation, a 20 mm endogastric overtube (EGT) was placed over a conical bougie with a preloaded ultrathin 5 mm endoscope (GIF-N-180, Olympus or EG1690K, Pentax) for safe introduction. Once the EGT had been introduced into the stomach, the conical bougie and the endoscope were removed before the EGT was fixed to the operating table to maintain a stable position.

The ACE stapler is an investigational device with an outer diameter of 16 mm that has a built in channel for the 5 mm endoscope. The stapler head is able to rotate 360 degrees and to articulate into complete flexion or retroflexion. A large piece of stomach tissue is acquired by applying a vacuum inside the silicon cover of the stapler head. The hydraulics in the stapler are activated to compress the tissue and a 10 mm plastic ring (polyetheretherketone, PEEK) with eight titanium staples is fired to create a large, full-thickness, transmural plication (Figure 5.2).

To create the first plication, the ACE stapler and the thin endoscope are advanced into the proximal stomach together and directed towards the greater curve of the proximal stomach wall. After plicating, the stapler head releases the tissue and is retracted together with the endoscope to preload a new staple cartridge. More plications are created in the stomach fundus by repeating the previous procedure. Reduction of

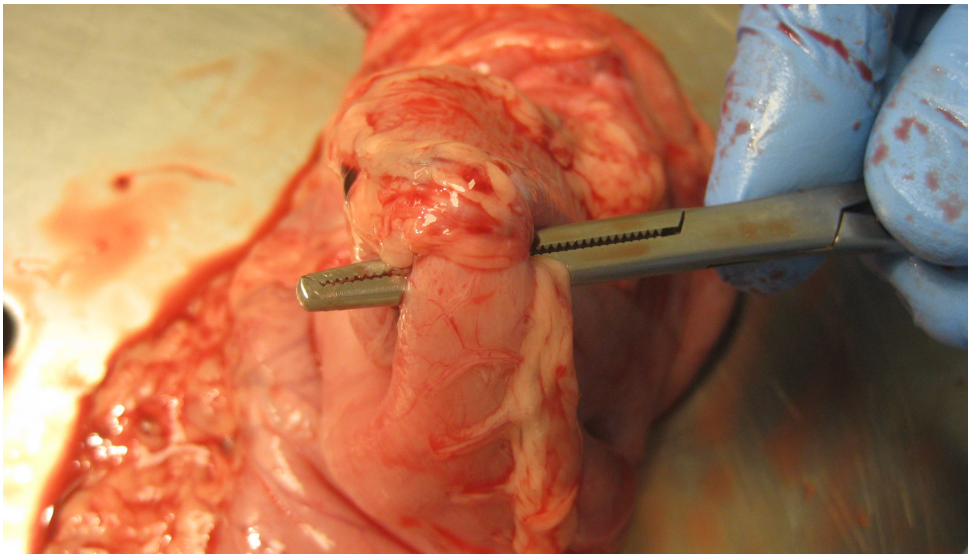


Figure 5.1 | *Demonstration of full thickness serosa apposition in a canine stomach*

the stomach volume along the greater curve is completed after creating a maximum of eight plications in the fundus and two additional plications in the antrum of the stomach. It is hypothesized that these two plications delay gastric emptying in addition to the volume reduction.

After completion of the procedure, the patient is monitored in the anesthesiology recovery area. All patients received intravenous analgesics (acetaminophen, diclofenac) and a proton pump inhibitor (PPI) to reduce postoperative pain and prevent acid reflux. Once patients were fully awake and stable, they were transferred to the ward for a planned overnight admission. Discharge criteria included the ability to tolerate liquids and adequate pain management with oral analgesics. At discharge, patients were instructed to follow a special diet to prevent excess pressure on the staple rings and allow the opposed tissue to fibrose. They were prescribed a liquid-only diet for the first two weeks, after which they were allowed a soft diet for two weeks before solid food was introduced. During follow-up, a dietician guided patients on a regular basis. In addition, they were instructed to eat small amounts, chew their food thoroughly and time their fluid consumption during and after meals.

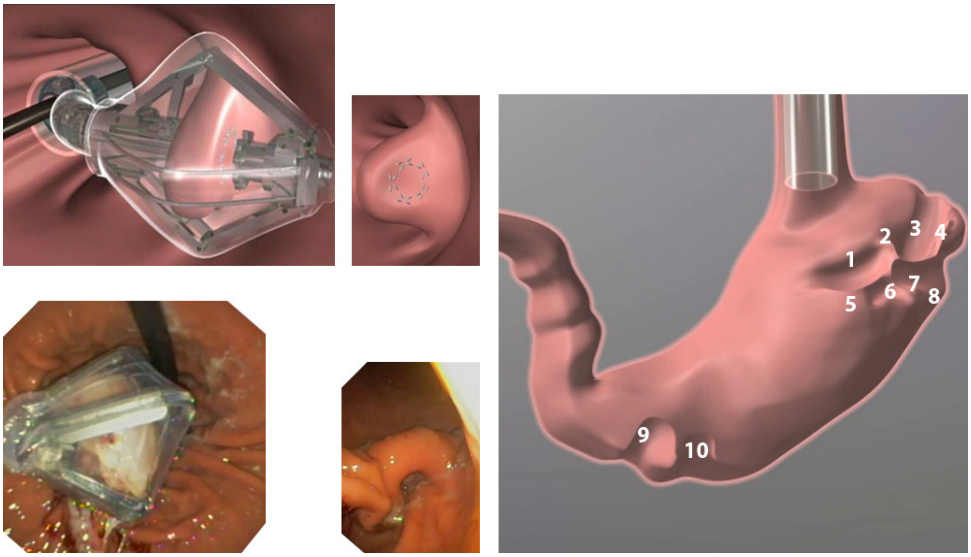


Figure 5.2 | *The tissue is acquired by vacuum in the stapler head before plications are stapled with a circular staple ring in 10 locations in the stomach.*

Setting

The study was performed at two university hospitals in the Netherlands (Academic Medical Center, Amsterdam, Maastricht University Medical Centre +). Follow-up office visits at the outpatient clinic took place at one week, and 1, 2, 3, 6, 9 and 12 months after the procedure. There were monthly telephone interviews in between office visits. Endoscopy was planned at the 12-month follow-up meeting.

Participants

The study's inclusion criteria were a BMI of 40–45 kg/m², or 30–39.9 kg/m² with one or more comorbidities expected to improve with weight loss. Participants aged 18–50 years with a history of failed standard non-surgical therapies could be included. It was mandatory that participants understand the risks of the procedure and were willing to participate in all aspects of the protocol for the duration of the study. Exclusion criteria included a history of gastro-duodenal ulcer disease, previous upper gastrointestinal surgery, hiatal hernia greater than 2 cm and significant esophageal disease. Moreover, patients with severe cardiopulmonary disease, poorly controlled diabetes mellitus, infectious disease, a history of cancer, Crohn's disease or ulcerative colitis, uncontrolled thyroid disease, renal insufficiency, hepatic insufficiency and alcohol or drug abuse were excluded. Patients unable to discontinue the use of aspirin and/or non-steroidal anti-inflammatory agents (NSAIDs) from 14 days prior to the procedure to 14 days post-procedure were excluded. Pregnant or lactating women were excluded, as well as patients with poorly controlled psychiatric disease or patients participating in another study at the same time. To prevent adverse events related to intubation and placement of the EGT, patients with a Mallampati classification greater than 3 were excluded. Written informed consent was obtained from all patients.

Outcome measurements

The primary endpoint was the feasibility and safety of the ACE procedure, expressed as the number of successful plication placements, serious adverse events and adverse events. The secondary endpoint was the efficacy of the ACE procedure, expressed as percentage of excess weight loss (%EWL; excess weight calculated using the Metropolitan Life Insurance Tables, midpoint of medium frame (18)), percentage of excess body mass index loss (%EBMIL; a normal BMI corresponds to a BMI of 25 kg/m²) and percentage of total weight loss (%TWL). Weight was documented during office visits at baseline and at 1, 2, 3, 6, 9 and 12 months. Other secondary endpoints were comorbidity reduction and eating behavior. Comorbidities were assessed by medication use

and blood pressure measurements at all office visits, while laboratory assessment was performed at baseline, 6 and 12 months.

Eating behavior was recorded at baseline and at 3, 6, 9 and 12 months using the TFEQ-R18 (Three-Factor Eating Questionnaire) (19, 20). Responses to each of the 18 items were divided into scores for cognitive restraint, uncontrolled eating and emotional eating. Raw scores on the TFEQ (1–4 or 1–8) were converted to a 0–100 scale. Higher scores in the respective factors indicate greater cognitive restraint, uncontrolled eating or emotional eating. The 'half-scale' method was used to compensate for missing data on some items (i.e. if more than half of the items for a scale were available, a metric average was allowed to be calculated) (19).

Data analyses and statistical analyses

Statistical analysis was performed with Prism 6.0 (GraphPad Software, Inc) and SPSS 19.0 (IBM Corporation, Somers, NY, US). For all patients, baseline data were compared to data acquired at follow-up visits. Because of a small sample size normal distribution of outcomes could not be assessed. Therefore, numerical variables were presented as median with an interquartile range (IQR) and tested using non-parametric tests, like Friedman's ANOVA and Dunn's multiple comparisons test for post-hoc analysis. Associations between two numerical variables were assessed with Spearman's correlation coefficient. Categorical variables were presented by number (%). A p-value ≤ 0.05 was regarded as statistically significant.

RESULTS

Participants

Between April 2012 and November 2012, 17 patients were screened. Four additional subjects (21 were anticipated) could not be screened because of financial restrictions of the sponsor. No patients were excluded after screening and written informed consent was obtained from all. Preoperative gastroscopy did not reveal any unexpected pathology. All included patients (11 female) with a median age of 37 years (IQR 32–48) underwent endoscopic gastric volume reduction. Median baseline BMI was 40.2 kg/m² (IQR 37.6–42.8). At baseline, nine patients had a BMI over 40 kg/m² and eight patients had a BMI between 30 and 39.9 kg/m² combined with at least one comorbidity. Comorbidities were dyslipidemia (n=4), hypertension (n=4), type II diabetes mellitus (n=2) and obstructive sleep apnea syndrome (OSAS; n=2) (Table 5.1). The ACE procedure

was completed in all 17 patients without perioperative adverse events. The maximum of 10 plications were created in seven patients; nine plications were created in the other 10 patients because the remaining space in their stomachs did not allow a tenth plication. The mean procedure time was 123 (IQR 95–129) minutes. Learning curve depended on the experience of the total team performing the procedure. The last three procedures were excluded from the analysis because of a new endoscopist. Procedure time was inversely correlated to procedure number (r=-0.736, p=0.01).

Postoperative upper-GI series clearly show the newly formed contours of the stomach with plications in the fundus and antrum indicating the reduced volume of the stomach (Figure 5.3).

	n=17
Female, no. (%)	11 (64.7)
Age at procedure, median (IQR), y	37 (32-48)
BMI, median (IQR), kg/m²	40.2 (37.6-42.8)
Obesity-related comorbidities, no. (%)	
Dyslipidemia	4 (23.5)
Hypertension	4 (23.5)
Diabetes mellitus type II	2 (11.8)
Obstructive sleep apnea syndrome	2 (11.8)

Table 5.1 | *Baseline characteristics. BMI: Body Mass Index (kg/m²), IQR: interquartile range; comorbidity data are presented as n (%) and median (IQR).*

Safety

Sixteen patients were discharged after one night; one diabetic patient was discharged after a second night to ensure adequate glucose regulation. No patient needed readmission and no serious adverse events occurred during the course of the study. Adverse events were gastric pain (n=7, range 1–3 days), sore throat (n=4, 2–3 days), diarrhea (n=4, 2–15 days), nausea (n=3, 2–4 days), constipation (n=4, 3–14 days), and vomiting (n=3, 1–4 days) (Table 5.2). All adverse events were mild and resolved with conservative treatment within 15 days after the intervention.

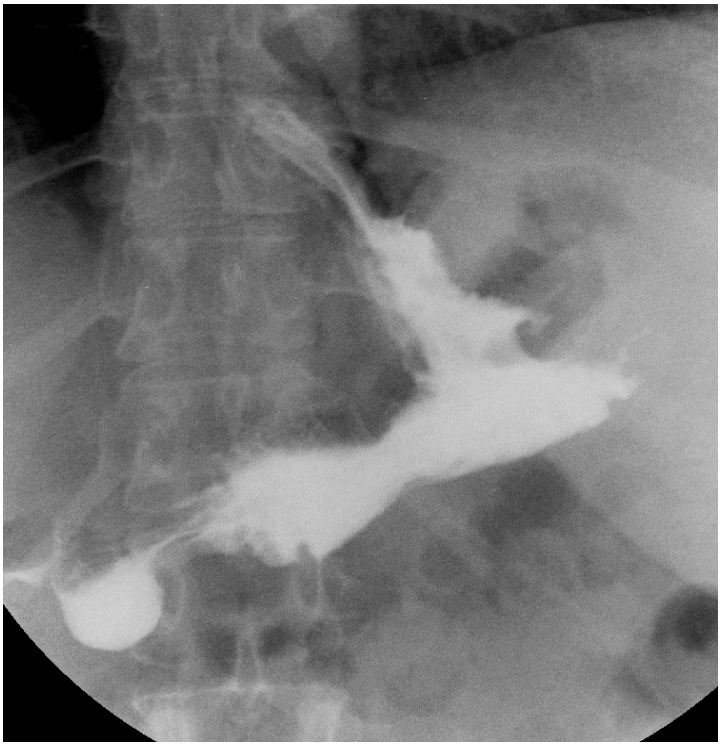


Figure 5.3 | *Upper GI series showing reduced stomach volume because of the plicated antrum and fundus.*

	Total number
Serious adverse events (n)	**0**
Adverse events (n)	
Gastric pain	7
Sore throat	4
Diarrhea	4
Nausea	3
Constipation	4
Vomiting	3

Table 5.2 | *Adverse events. All adverse events were mild or moderate and could be treated conservatively.*

Weight loss

Up to six months follow-up data is available for 100% of patients. At 12 months 88.2% is available. All 9-month data as well as the 12-month study data for two patients are missing because the study was temporarily interrupted due to the study sponsor's (BaroSense, Inc.) financial problems. These patients continued follow-up when the assets of the company were acquired and a new sponsor (Boston Scientific Corporation) restarted the study. Due to personal problems, one patient did not attend office visits for several months. Median BMI dropped significantly, from 40.2 kg/m² (IQR 37.6–42.8) to 34.5 kg/m² (IQR 30.2–36.7, p=0.000) in the first year. The median percentage of excess weight loss at 1, 3, 6 and 12 months was 16.0% (IQR 12.6–20.2), 22.2% (IQR 17.1–32.9), 25.6% (IQR 22.9–37.9) and 34.9% (IQR 17.8–46.6), respectively (Figure 5.4).

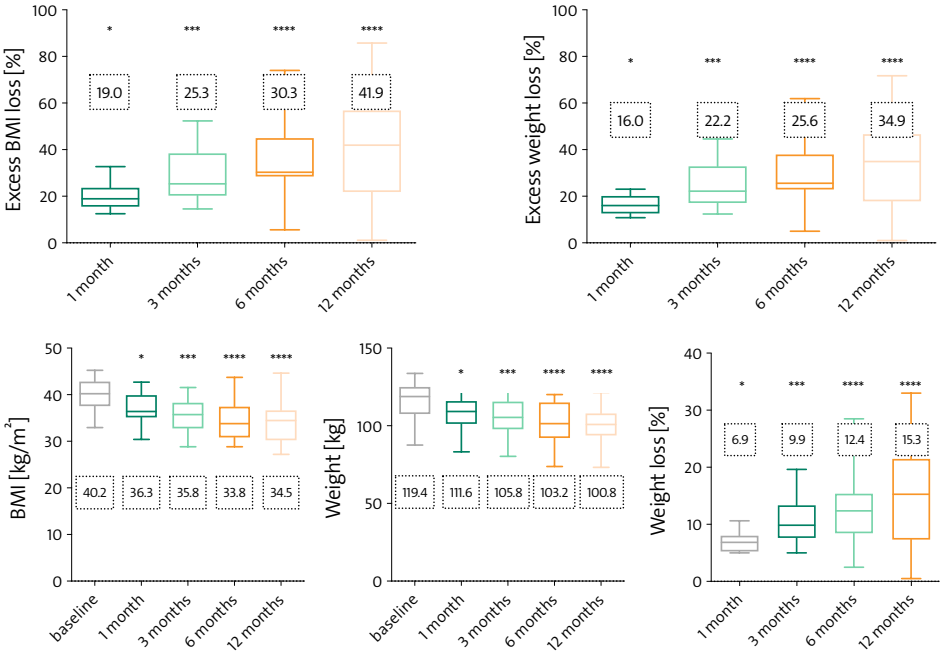


Figure 5.4 | *Weight loss graphs expressing excess BMI loss, excess weight loss, BMI, weight and weight loss percentage in the first year after the procedure. True median values are in the dotted boxes. *p<0.05 ***p<0.001 ****p<0.0001*

Comorbid diseases

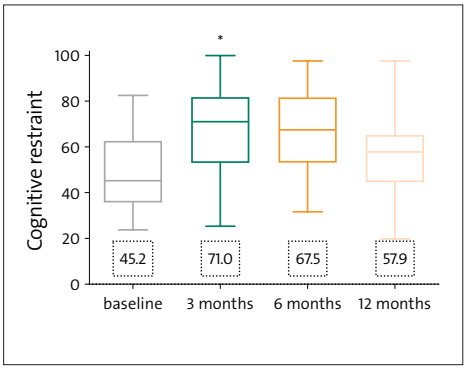
At 12 months, dyslipidemia resolved in three of four patients and improved in one (normalized lab but still on medication). The remission rate for hypertension was 50% (2/4). Both DMII patients could reduce oral medication and cease (n=1) or reduce (n=1) insulin use. OSAS was in remission for one out of two patients.

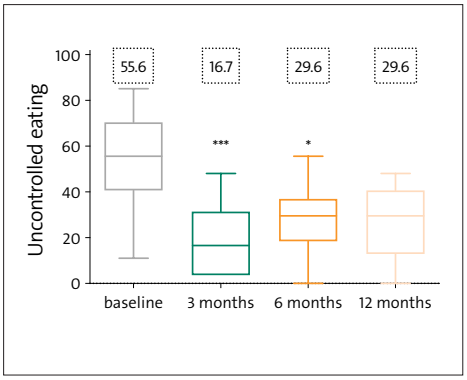
Eating behavior

The TFEQ was completed before the procedure and after 3, 6 and 12 months. At 12 months, eating behavior data was available for 12 patients but two did not complete the list at baseline, which made statistical testing possible for only 10 subjects. TFEQ results showed a significant change in eating behavior on all three factors: while there was an increase in cognitive restraint, uncontrolled eating and emotional eating decreased. The largest differences on all factors were found after three months. After 6 months, the uncontrolled eating score was still decreased, while emotional eating and cognitive restraint were getting closer to baseline values (Figure 5.5). There was one item missing in the nine-item uncontrolled eating scale for one subject at one moment.

Endoscopic evaluation

Endoscopy was performed in 11 patients at 12 months to evaluate the gastric anatomy (Figure 5.6). The endoscopists experienced a significant volume reduction when insufflating during endoscopy. Although exploration time was limited for patient comfort, the majority of plications (6–9) were identified in all subjects. No signs of ulceration or necrosis were seen in the stomachs. One patient had a Barrett's segment in the esophagus that showed high-grade dysplasia in one of the biopsies taken during endoscopy. Reviewing the video of the procedure one year earlier, we found that the segment had already been present but had not been recognized as Barrett's esophagus.





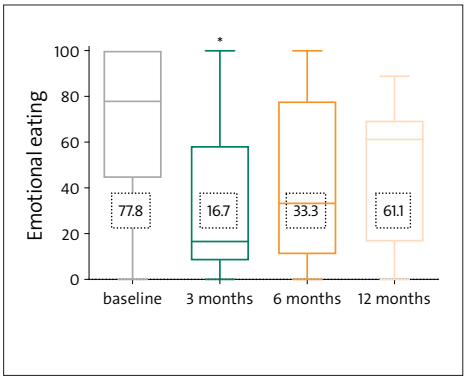
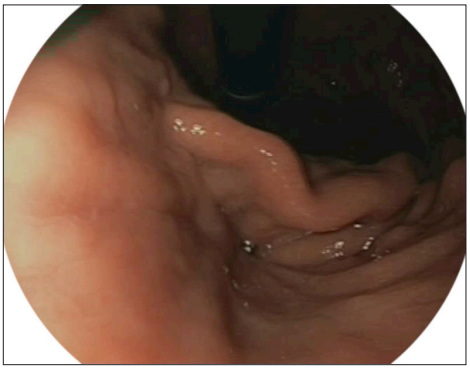
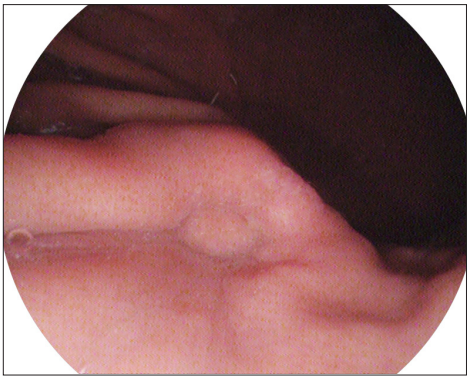


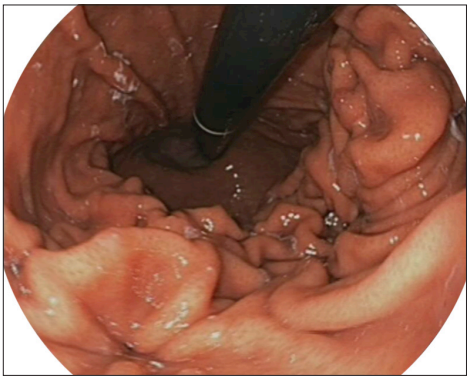
Figure 5.5 | *Eating behavior expressed as cognitive restraint, uncontrolled eating and emotional eating as assessed by the TFEQ-18. True median values are in the dotted boxes. *p<0.05 ***p<0.001*



A



B



C

Figure 5.6 | *12-month endoscopy. A: clear endoscopic view at one of the plications; B: close-up at one of the staple rings; C: reduced space in the fundus.*

DISCUSSION

ACE stapling is an endoscopic procedure that reduces the volume of the stomach. This advanced system, with a wide range of motion in the stapler head, allows physicians to create plications in the desired locations without too much effort. Although access to the stomach of the EGT is easier in the dog, the canine model was extremely useful to train physicians. The canine stomach tissue behaved much like human tissue. Because stomach volume reduction is performed via the oral route, there is no need to transect abdominal structures and the stomach tissue is acquired with atraumatic suction on the stomach wall. These characteristics minimize the risks of gastrointestinal leaks, perforation and infection. The theoretical risk of obstruction when the plicated proximal stomach would slip into the hiatus was minimized by excluding subjects with a hiatus hernia > 2cm.

This first reported human Phase 1 study shows the ACE procedure is safe and that adverse events are mild and can be treated conservatively. In this uncontrolled study, treated patients also showed significant weight loss over 12 months and improved control over eating behavior. One hundred and sixty plications were created in 17 patients without significant problems and endoscopy 12 months after the procedure suggested the plications were durable.

Limiting the ability of the stomach to expand by reducing its volume, particularly in the region of the fundus, and impeding the receptive relaxation after food intake, leads to early feelings of fullness and enhanced satiety. Food intake is controlled by the ventromedial nucleus of the hypothalamus, which is influenced by gut hormones, glucose levels and neuronal input from the vagus nerves. The stomach contains many nutrient-sensing cells, has stretch receptors to give feedback on fullness and is capable of increasing or reducing production of ghrelin (the hormone related to hunger). In this Phase I study, we did not measure neurohumoral factors. In future studies, evaluation of these hormones will determine whether an association with the weight loss induced by ACE exists.

In the previously studied TERIS procedure, in which a small pouch is created in the proximal stomach by attachment of a silicone restrictor to anchors in the stomach plications, preliminary weight loss results were promising (15). However, detachment of anchors was seen in prolonged follow-up. A perforation and pneumoperitoneum occurred in the first patients, necessitating changes in the system that resulted in an improved safety profile. The ACE stapler was developed while maintaining the safe

technique to create only stomach plications. Compared to TERIS, the ACE stapler has the advantage that no foreign body is implanted so no removal procedure is necessary. Furthermore, a smaller, 20 mm EGT can be used.

Several other new minimally invasive endoscopic procedures are currently under investigation (17, 21, 22). The earlier-mentioned EndoBarrier excludes the proximal intestine and has an effect on glucose regulation and gastrointestinal hormone responses (23). This is a different mechanism of effect, but there are other studies describing endoscopic restrictive procedures. Fogel et al. performed endoluminal vertical gastroplasty (EVG, EndoCinch Suturing System, C.R. Bard, Murray Hill, NJ, US) in 64 patients (24). In EVG suturing, the posterior and anterior walls of the stomach together create a vertical lumen. Familiari et al. reported 12-month data on the TOGA (transoral gastroplasty; Satiety Inc., Palo Alto, CA, USA) procedure, in which a vertical sleeve is created along the lesser curve of the stomach using two stapling devices (25). One short-term study was recently published on the POSE technique, which resembles the ACE procedure. An autosuture device is used to create 8-9 full-thickness plications in the fundus and 3-4 in the distal body after approximating a tissue fold with a jawed gripper.

All reported studies have excellent safety profiles and TOGA and EVG were performed as outpatient procedures, while patients in the POSE study were discharged after 12 to 24 hours. In the ACE procedure reported in this article, adverse events were also minimal and overnight observation was purely a safety measure. A new larger study will not require routine overnight observation. Altogether this resembles a high safety profile among the four endoscopic procedures. Weight loss results are good and comparable to the results of the ACE study or even better. The TOGA procedure reports 29.3% and 38.7% excess weight loss at 3 and 12 months and the EVG 39.6% and 58.1%, respectively. The POSE study reports 49.4% excess weight loss after 6 months, although their method of excess weight calculation (actually excess BMI loss) overestimates the effect.

Success of the endoscopic procedures will depend on the long-term effects and durability of the volume reduction. During EVG follow-up, endoscopy was performed in 14 out of 64 patients at random time points between 3 and 12 months after the procedure. Of these 14 patients, nine showed either loose stitches or complete disruption of stitches. For TOGA, dehiscence of the staple line was observed in almost half of the cases. The POSE procedure only has 6 month follow-up and does not report the outcome of follow-up endoscopy, although one image of an intact plication at 6 months follow-up is presented. In contrast to the procedures described by both Fogel et al. and Familiari et al., the plications in the POSE and ACE technique are full-thickness serosa-serosa plications. This may promote better long-term durability since mucosa-mucosa

apposition is a much more fragile construction. In contrast to serosa, mucosa is in a constant renewal process, preventing the development of dense fibrous appositions (26). Another difference from the other procedures is the manipulation of the greater curvature, which may create better durability because it is more flexible than the rigid lesser curvature. In the present study, durability was confirmed as the majority of plications were recognized in all performed endoscopies one year after the procedure. The long-term follow-up results of the POSE technique have to be awaited for evaluation of the durability.

The handling of the device is relatively straightforward. The challenge is to adequately determine the desired location for the plications in a relatively small cavity with impaired vision. A technical drawback of the current design is that an experienced engineer is needed to reload the stapler after every plication. This maneuver takes up to seven minutes each time before reentering the stomach, determining the next location and creating a new plication. A stapler that allows stapling more than one plication in the same field of view without reloading would reduce procedure time dramatically. Currently the procedure can be performed in approximately 90–100 minutes in experienced hands. Without the frequent reloading, 45 minutes may be a realistic estimate, much faster than the 60–140 minutes needed for other published gastric plication techniques (21).

Patients are usually highly motivated when starting new weight loss attempts, whether this is a low-calorie diet, exercise or an operative procedure. Motivation is further increased by regular follow-up by the research team. This probably gives patients more control over their eating habits initially, but would lead to recurrence of old behavior in the longer term. This is recognized in the changes in eating behavior reported in the TFEQ. Patients were experiencing better cognitive restraint, less uncontrolled eating and less emotional eating in the first three to six months, but regained problems with emotional eating and cognitive restraint at 12 months. It is, however, promising that uncontrolled eating was still low at 6 and 12 months. Some follow-up data was missed due to the transfer of the technique to a new sponsor. Therefore, the data is not complete for all 17 subjects and the nine-month follow-up point was lost for everyone.

In conclusion, this first human application of the ACE stapler suggests the procedure is safe and results in significant weight loss. In the next phase, there should be a multi-fire stapler design and the procedure can be done as an outpatient procedure. A randomized (sham controlled) and long-term follow-up on weight and adverse events is needed to determine its place in the treatment spectrum of the obese patient.

Funding

The study was funded by BaroSense, Inc. until sufficient funds could no longer be raised and the company had to stop their activities. Boston Scientific Corporation recently acquired their assets and is in the process of restarting data collection. Funding for the two-year follow-up will be provided by Boston Scientific Corporation.

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5.1

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Comment and Response to Chapter 5

GASTRIC RESTRICTION AND DELAYED GASTRIC EMPTYING MAY NOT BE THE KEYS TO AN EFFECTIVE ENDOSCOPIC METABOLIC THERAPY

To the Editor:

We read with interest the recently published article by Verlaan and Paulus et al (1) describing the use of an endoscopic stapler for gastric volume reduction in obese patients. As the authors point out, studies of several other gastric restrictive techniques have reported similar outcomes (2-5). When the outcomes of endoscopic restrictive therapies are analyzed, the reduction in obesity-related comorbidities appears to correlate with the degree of weight loss. In comparison, the benefits of vertical sleeve gastrectomy (VSG) go beyond its ability to simply produce weight loss (6). VSG is now recognized to alter critical signaling and metabolic pathways to improve the metabolic profile even before significant weight loss occurs, indicating that it is more than simply a restrictive procedure (7,8).

This raises mechanistic questions as to why VSG has superior outcomes compared with endoscopic restrictive therapies. One obvious difference is the excision of 80% of the gastric mucosa in VSG. The gastric mucosa is being increasingly recognized as an important regulator of hunger and food intake (9). Therefore, if endoscopic techniques are targeted at impeding the function of the gastric mucosa, could one expect an improvement in comorbidities out of proportion to simply weight loss?

A misconception held by many is that delayed gastric emptying results in reduced caloric intake. In this study, 2 plications were placed in the antrum with the specific purpose to decrease gastric emptying [1]. However, gastric emptying appears to be accelerated after VSG, and this has been suggested as a mechanism for its improvement in metabolic profile (10).

Understanding the mechanisms contributing to the benefits of VSG offers tremendous potential to develop an endoscopic metabolic therapy. Progress toward this goal has been hindered because many continue to ignore the true science behind the benefits of bariatric surgery, a technique that has been proved to reduce obesity-related morbidity and mortality.

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RESPONSE

We thank Kumbhari et al for their interest in our recent publication "Endoscopic gastric volume reduction with a novel articulating plication device is safe and effective in the treatment of obesity" in Gastrointestinal Endoscopy (1), but we believe a reply to their letter is justified.

We support the statement that understanding the mechanisms behind obesity and weight loss surgery will contribute to the development and improvement of new techniques. Gastric emptying rate is clearly a piece of this puzzle and is exactly the reason why plications were also created in the antrum. Several studies have investigated the role of gastric emptying in the development of obesity and have found that obese people have enhanced gastric emptying, that delayed gastric emptying is linked with increased feelings of satiety, and that another effective minimally invasive restrictive therapy - the intragastric balloon - is accompanied by delayed gastric emptying (2-5). Therefore, we cannot agree with the statement by Kumbhari et al that this is a misconception.

The simple fact that, in some studies, the gastric emptying rate is increased after laparoscopic sleeve gastrectomy (LSG) does not mean that this solely enhances weight loss. Because a large portion of the stomach is removed, one could also argue that LSG is effective despite an enhanced gastric empting rate because of the extreme effects of volume reduction and removal of ghrelinproducing cells. Endoscopic gastroplication of the fundus aims to reduce the capacity of the stomach, thereby interfering with gastric accommodation and relaxation after meal ingestion, contributing to a sense of fullness. Plicating the antrum in our procedure aims to limit enhanced gastric emptying caused by the gastric volume reduction. The procedure is minimally invasive and has an exceptional safety profile compared with LSG (6). Because bariatric surgery should be applied only if the expected health improvement outweighs the risk of surgery, a safer risk profile makes endoscopic techniques accessible to a broader group of patients.

To understand the exact mechanisms behind weight loss after endoscopic gastroplication, we additionally studied gastric emptying, GI hormone changes, and feelings of hunger and satiety in a subgroup of 10 patients. The results of this study will be submitted for publication soon and will demonstrate short-term and long-term changes that are not explained by weight loss alone.

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Endoscopic Gastroplication for Morbid Obesity. Effects on Reduction of Food Intake and Gut Hormone Profile after 1 Year of Follow-Up.

ABSTRACT

OBJECTIVE

To asses the effects of endoscopic gastroplication on food intake, hunger and fullness, gastrointestinal (GI) motility and the release of ghrelin, GLP-1 and PYY.

DESIGN

Ten adult morbidly obese patients (6 males; mean BMI: 39.8 ± 0.9 kg m^2) underwent gastroplication with the endoscopic stapler. Patients were studied before, one month and twelve months after the procedure.

RESULTS

Excess body weight decreased with 14.4±1.3% one month after the procedure, and progressed to 37.9±4.8% after twelve months

(p<0.001). Ad libitum food intake decreased one month after the procedure compared to baseline (BL: 854±94 vs 1M: 446±43 kcal, p < 0.01), but increased towards baseline at twelve months (12M: 603±64 vs 1M: 446±43 kcal, p < 0.05). Fasted concentrations of GI peptides increased 12 months after the procedure (ghrelin; BL: 46.5±5.9 vs 12M: 63.4±5.2 pg/mL p<0.001, GLP-1; BL: 1.97±0.32 vs 12M: 3.87±0.38 pM, p<0.01 and PYY; BL: 63.3±6.7 vs 12M 78.9±8.6 pg/mL; p<0.01). No differences in gastric emptying half time ($t_{1/2}$) or orocaecal transit time were observed.

CONCLUSION

Gastroplication with the ACE stapler resulted in a reduction of ad libitum food intake and decrease in hunger feelings partially paralleled by changes in GI peptides, without influencing gastric emptying rate.

INTRODUCTION

The global overweight and obesity epidemic is turning into an enormous economic and healthcare burden. Currently, over 1.9 billion adults suffer from overweight or obesity worldwide. To date, the only effective long-term treatment strategy for morbidly obese people is bariatric surgery (1-3). The most commonly performed procedures such as Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG), result in approximately 60-70% excess weight loss and lead to effective reduction of obesity related diseases, but are associated with considerable morbidity (1, 4-6). Compared to other therapies, bariatric surgery is a drastic measure and only indicated when the expected improvement in health outweighs the risk of surgery. Hereby, a substantial group of patients with less severe obesity or a higher complication risk cannot benefit from these procedures. There is need for novel minimal invasive surgical or endoscopic techniques that also result in substantial weight loss but have a safer risk profile compared to the traditional bariatric procedures.

One of these new techniques is the Articulating Circular Endoscopic (ACE) stapler for gastric volume reduction. During this transoral endoscopic procedure several gastric plications are created to reduce the volume of the stomach. Recently, data from the first human study showed that the procedure is safe and results in a promising excess weight loss of 35% in the first year (7). It is hypothesized that the procedure induces limitation of the stomach to expand during food intake, which leads to a faster onset and more pronounced feeling of fullness and satiation thereby influencing food intake. Although an effect on food intake after ACE has been demonstrated, the mechanisms of action have not been studied. It has been emphasized in recent publications that alterations in gastrointestinal transit time and the release of gut derived peptides play a key role in the amount of weight loss after bariatric surgery. Changes in gastric emptying (8-10), ghrelin (11), GLP-1 and PYY (12, 13) have been reported after traditional restrictive procedures such as laparoscopic adjustable gastric banding (LAGB) and LSG and during the temporary placement of an intragastric balloon.

The aim of this prospective study was to assess the effect of the ACE stapler procedure on food intake, postprandial satiation, gastric emptying and the release of gastrointestinal peptides (ghrelin, GLP-1 and PYY). Before, 1 month after and 1 year after ACE subjects underwent a standardized meal satiety test. We hypothesize that the restrictive ACE stapler procedure inhibits food intake and gastric emptying, alters gastrointestinal peptide release and increases post-prandial satiety.

METHODS

Subjects

All ten patients that were treated in our center were included in this study. Written informed consent was obtained from each individual before inclusion. This study was approved by the Medical Ethics Committee of the Maastricht University Medical Center+ Maastricht, the Netherlands, and performed in full accordance with the Declaration of Helsinki. The study has been registered in the US National Library of Medicine (http://www.clinicaltrials.gov, NCT02381340).

ACE procedure

The ACE stapler has a silicone cap, which uses vacuum to acquire tissue and place it between the stapler arms. The stapler is inserted to the stomach together with an endoscope through the esophagus, after which up to ten full-thickness plications are created in the fundus and antrum. Aim of the procedure is to induce volume restriction, without the need of a laparoscopic approach. The technique is described in detail in the original paper (7).

Study outline

Patients were studied on three occasions: preoperatively (indicated as baseline, BL), at 1 month (1M) and 12 months (12M) postoperatively. Test days were identical and started in the morning after a 10-hour overnight fast with the placement of an antecubital intravenous catheter (see Figure 6.1 for design of test day). At 8.30 AM (t = -15) blood and breath samples were obtained and Visual Analogue Scores (VAS) for hunger and fullness were assessed. Subsequently a standardized breakfast meal, consisting of a sandwich and an egg (sunny side up, 210 kcal), was consumed with 250 mL of tap water. The total volume of the meal was approximately 380 mL. Breath samples were collected to determine gastric emptying rate and duodenocecal transit time (details below); since it was hypothesized that plicating the stomach could alter GI transport. Venous blood draws, VAS and breath samples were repeated at regular intervals during the test day. Four hours after the ingestion of the breakfast meal, subjects received a standardized ad libitum lunch meal (Lasagna Bolognese; Plus Supermarkt, Maastricht, the Netherlands; energy density per 100 gram: 160 kcal, 7.1 g protein, 11.0 g carbohydrates and 9.4 g fat). A final VAS score was obtained after ingestion of the lunch meal before subjects returned home.

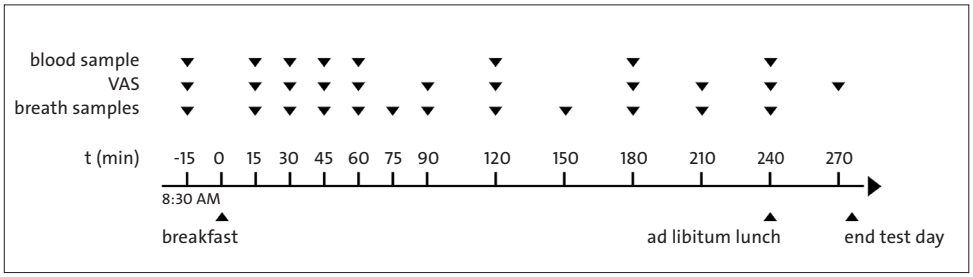

Figure 6.1 | *Timeline of test day. Blood samples, visual analogue scale (VAS) scores and breath samples were collected at the indicated time points.*

Hunger and fullness scores

Scores for hunger and fullness were measured using VAS (0 to 100 mm), anchored at the low end with the lowest intensity feelings (e.g. not hungry/full at all), and with opposing terms at the high end (e.g. extremely hungry/full) (14).

Gastric emptying

Gastric emptying was determined by using the 13C stable isotope breath test (15). 13C-octanoic acid (100 mg, Campro Scientific bv, Veenendaal, the Netherlands) was mixed into the standardized breakfast meal ingested at t=0. Breath samples of $^{13}CO_2$ were obtained at baseline and at 15, 30, 45, 60, 75, 90, 120, 150, 180, 210 and 240 minutes after ingestion of the breakfast meal and analyzed by using Isotope Ratio Infrared Spectometry (IRIS, Wagner, Bremen, Germany) (16). The Ghoos model was used in order to calculate gastric emptying half time and lag time (15).

Orocaecal transit time

Orocaecal transit time was determined by the lactulose hydrogen breath test, as described by Ledeboer et al (17). Six grams of lactulose (Legendal, Inpharzam, Amersfoort) were dissolved in the water consumed directly after finishing the breakfast meal. Breath samples were taken at 15 min intervals and analyzed using a handheld hydrogen breath test unit (Gastyrolyzer, Bedfont Scientific, Kent, United Kingdom). Small bowel transit time was defined as the time between lactulose administration and the onset of a sustained rise in breath hydrogen concentration of at least 10 parts per million (ppm) above basal level.

GI peptides

Blood samples were collected in ice chilled EDTA with aprotinin coated tubes for GLP-1 and PYY (Becton, Dickinson and Company, Plymouth, UK). Immediately after blood collection, DPP-IV inhibitor (Millipore, Massachusetts, USA) was added to the tubes to prevent proteolytic cleavage (10 µL/mL blood). Regular EDTA-coated tubes were used to collect blood for ghrelin measurements. Tubes were immediately centrifuged at a rate of 3000 rpm and 4° C for 15 min, after which plasma was transferred into aliquots and stored on dry ice. For ghrelin analysis, serine protease inhibitor phenylmethylsulfonyl fluoride (dissolved in methanol and hydrochloric acid) was added to the plasma. Samples were stored at -80° C until the moment of analysis.

Plasma PYY (full length PYY1–36 and fragment PYY3–36) and GLP-1 (7-36 and 9-36) were measured by enzyme-linked immunosorbent assays (Millipore, Massachusetts, USA) in an experienced laboratory (18). Active ghrelin was measured by an established in-house radioimmunoassay (Millipore, Massachusetts, USA) (19).

Statistical analyses

Statistical analyses were performed with Prism 6.0 (GraphPad Software, Inc. La Jolla, CA). Curves for VAS scores and hormone responses were analyzed with 2-way repeated measures ANOVA. A post-hoc Tukey test for multiple comparisons was used to analyze differences at specific time-points. Total scores and hormone levels in the 240 min timeframe (i.e. total hunger, total ghrelin) were expressed as area under the curve (AUC), calculated by the trapezoid rule and analyzed with one-way repeated measures ANOVA (Tukey's test for post-hoc analysis). Incremental cumulative areas under the curve (iAUC) were used to detect meal-induced changes using the trapezoid rule. Pearson's R correlations were calculated between VAS scores and food intake, hormone levels and food intake and changes in VAS or hormone levels and food intake between follow-up moments (delta VAS/hormone, delta food intake). Data are presented as the mean ± SEM (unless specified otherwise). A p-value < 0.05 was considered significant.

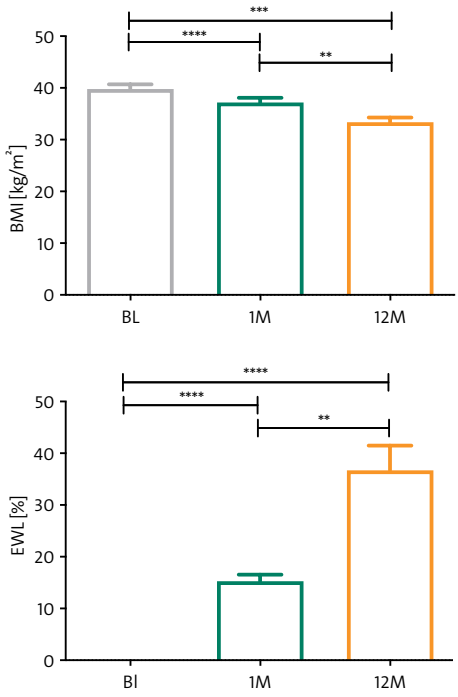

Figure 6.2 | *BMI (kg/m²) and EWL (%) (mean +SEM) of the ten morbidly obese subjects during baseline (BL), one month (1M) and twelve months (12M) postoperatively. ** p<0.01, *** p<0.001, **** p<0.0001*

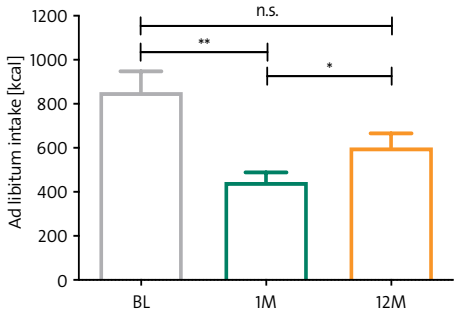

Figure 6.3 | *Food intake in kcal (mean+SEM) of the ad libitum lasagna lunch ingested at the end of the test day during baseline (BL), one month (1M) and twelve months post-procedural (12M), respectively. * p<0.05, ** p<0.01.*

RESULTS

Effect of ACE stapling on body weight

At baseline, patients (6 males, 4 females) were 39±2 years old and weighed 119.3±3.5 kg with a BMI of 39.8±0.9 kg/m². Excess body weight had decreased by 14.4±1.3% one month after the procedure, corresponding to 8.2±0.5 kg weight loss or 2.8±0.2 kg/m² BMI reduction (p<0.0001). Weight had further decreased after twelve months by 19.1±2.8 kg (BMI loss 6.5±1.0 kg/m²), equivalent to 37.9±4.8% excess weight loss (p<0.001) (Figure 6.2). Subjects experienced only mild and transient adverse events after the procedure, as reported previously (7).

Food intake

Ad libitum food intake decreased one month after the procedure compared to baseline (BL: 854±94 vs 1M: 446±43 kcal, p < 0.01). However, ad libitum food intake twelve months after the procedure increased significantly towards baseline compared to one month post-procedural (12M: 603±64 vs 1M: 446±43 kcal, p < 0.05). There was no statistically significant difference left between baseline and twelve months postoperatively (p=0.07) (Figure 6.3).

Hunger and fullness after ACE stapling

Mean VAS scores for hunger and fullness are given in Figure 6.4. Fasting hunger scores at baseline did not differ between the three time points (Figure 6.4a). Fasting scores for fullness at 1 month after the procedure were significantly higher compared to baseline ($p<0.05$) (Figure 6.4b). Consumption of the breakfast increased fullness and decreased hunger in all three occasions. The AUC (-15 to 240 min) for hunger at baseline was significantly higher compared to 1 month ($p<0.01$) but not compared to 12 months. Furthermore, the AUC for hunger 1 month postoperatively differed significantly from 12 months postoperatively (Figure 6.4c). The AUC (-15 to 240 min) for fullness at baseline was significantly lower compared to 1 month ($p<0.01$) and 12 months ($p<0.05$) postoperatively. However, it was significantly lower at 12 months compared to 1 month

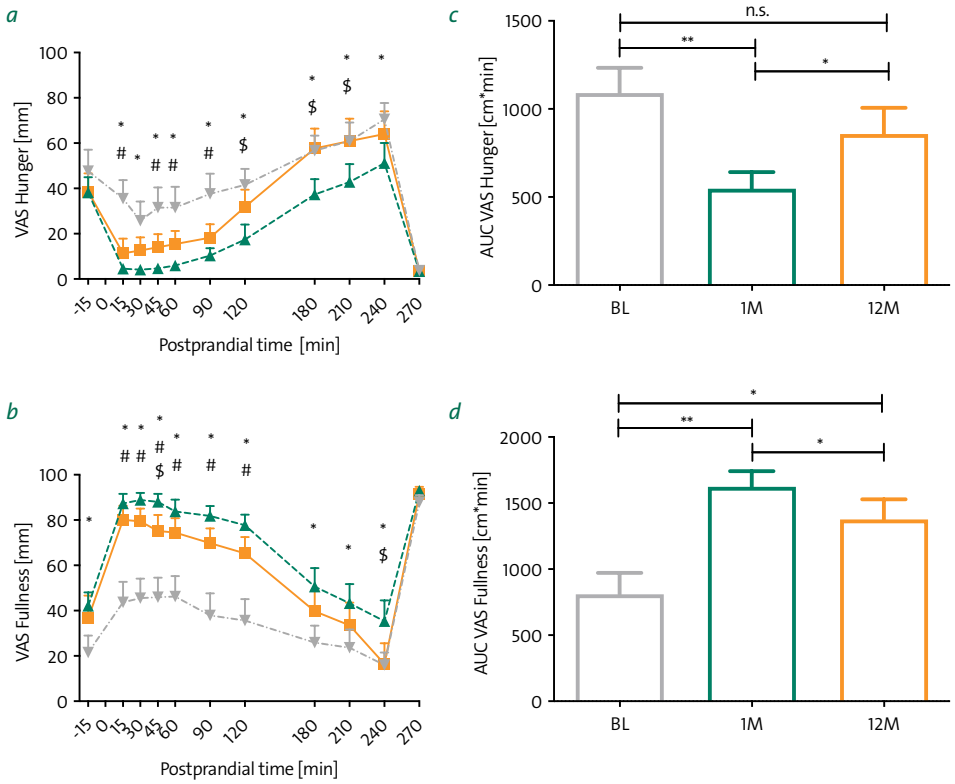

Figure 6.4 | *Hunger (mean+SEM) and fullness (mean+SEM). VAS hunger and fullness areas under the curve during baseline (BL), one month (1M) and twelve months (12M) post-procedural, respectively. Breakfast was consumed at t=0 and the ad libitum lunch was offered at t=240 min. AUCs were calculated using the trapezoid rule. * p<0.05 BL vs 1M, # p<0.05 BL vs 12M, $ p<0.05 1M vs 12M * p<0.05 and ** p<0.01.*

(p<0.05) (Figure 6.4d). Total AUC for hunger and satiety (from -15 to 240) or hunger and satiety at t=240 were not correlated to ad libitum food intake at any follow-up moment, nor were delta hunger and delta fullness scores correlated tot delta ad libitum intake after 1 or 12 months.

GI peptide profiles change after ACE stapling

Ghrelin (Figure 6.5).

Twelve months after the procedure, fasted ghrelin levels (but not total AUC for ghrelin) were increased compared to baseline (BL: 46.5±5.9 vs 12M: 63.4±5.2 pg/mL p < 0.001). Breakfast at t = 0 induced a significant decline in plasma ghrelin levels at both 1 month and 12 months postoperatively, that was absent at baseline (iAUC-15-45 BL: 6.9±8.5 vs

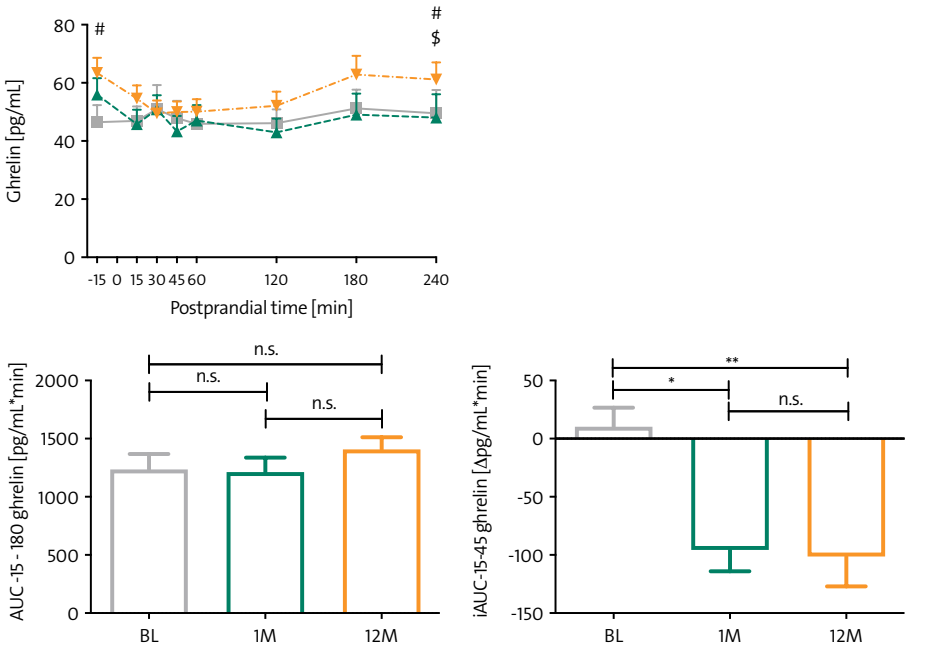

Figure 6.5 | *Ghrelin concentrations (mean+SEM) and ghrelin area under the curve (for t=-15-150 min and t=-15-45 min) during baseline (BL), one month (1M) and twelve months (12M) post-procedural, respectively. # p<0.05 BL vs 12M, $ p<0.05 1M vs 12M,* p<0.05, ** p<0.01.*

1M: 35.1±11.3 vs 12M: 36.1±10.7 Δpg/mL*min; BL vs 1M $p < 0.05$; BL vs 12M $p < 0.01$). After the initial decline, ghrelin levels increased towards fasted values in all the occasions. The plasma ghrelin levels before the ad libitum meal were not associated with caloric intake at any moment, nor was delta total ghrelin or delta ghrelin at t=240 min correlated to delta food intake.

PYY (Figure 6.6a).

One month after the procedure, fasted PYY levels were lower compared to baseline (1M: 46.9±6.2 pg/mL vs BL: 63.3±6.7; $p < 0.01$), while an increase was observed after twelve months compared to both baseline and 1 month (12M 78.9±8.6 pg/mL; both $p < 0.01$). The AUC for PYY was not different after 1 month compared to baseline, but was increased after 12 months compared to both baseline and 1 month (BL: 762.5±89.2 vs 1M: 661.2±88.0 vs 12M: 1134±97.1 pg/mL*min, both $p < 0.05$).

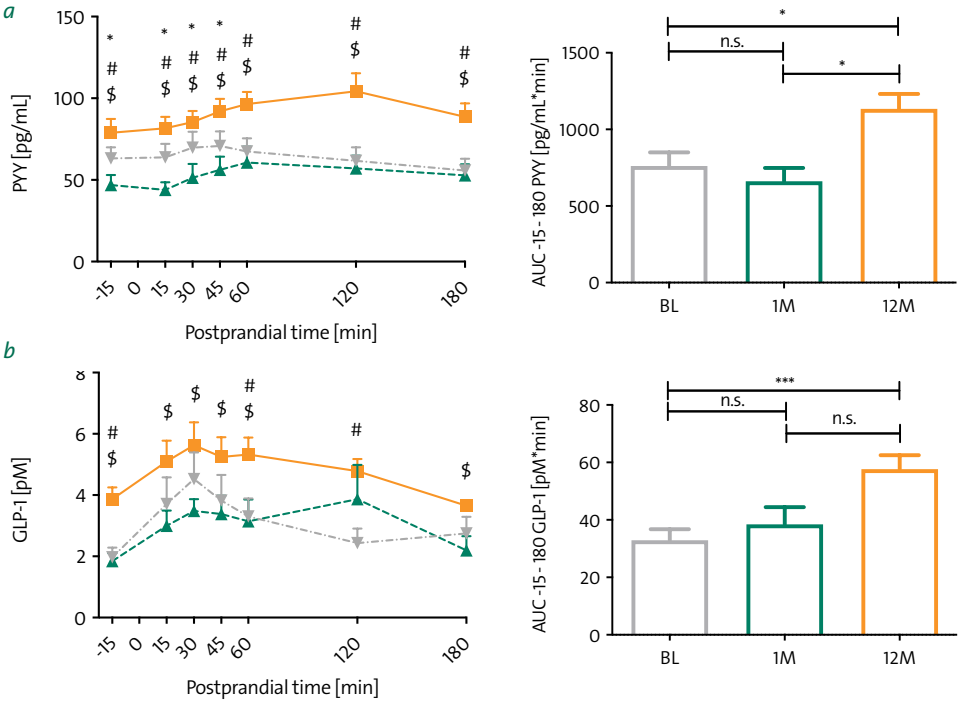

Figure 6.6 | *PYY and GLP-1 concentrations (mean+SEM) and area under the curve (for t=-15-180 min) during baseline (BL), one month (1M) and twelve months (12M) post-procedural, respectively. * p<0.05 BL vs 1M, # p<0.05 BL vs 12M, $ p<0.05 1M vs 12M * p<0.05, *** p<0.001.*

GLP-1 (Figure 6.6b).

12 months after the procedure, fasted GLP-1 levels were significantly higher compared to baseline and 1 month (BL: 1.97±0.32 vs 1M: 1.85±0.25 vs 12M: 3.87±0.38 pM, both $p < 0.01$). The AUC for GLP-1 only increased twelve months after the procedure compared to baseline (BL: 32.9±3.9 vs 12M: 57.7±4.8 pM*min, $p < 0.001$).

Gastro intestinal transit

The procedure did not result in statistically significant differences in gastric emptying half time ($t_{1/2}$), lag time or orocaecal transit time after 1 or 12 months (Figure 6.7).

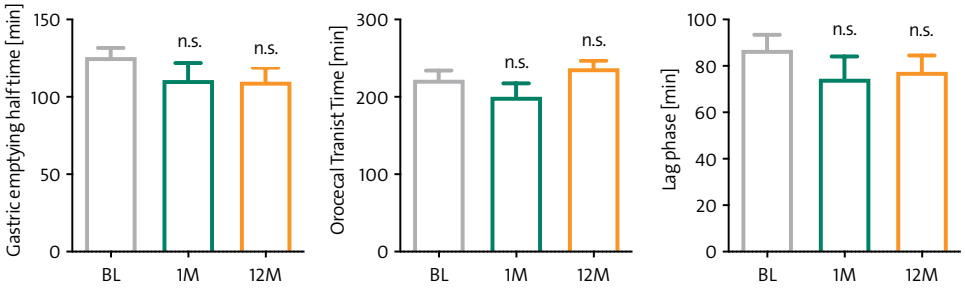

Figure 6.7 | *Gastric emptying half time (min), lag phase (min) and orocecal transit time (min) (mean+SEM) during baseline (BL), one month (1M) and twelve months (12M) post-procedural, respectively. No statistically significant differences between the test days were found.*

DISCUSSION

In this study we have shown that endoscopic gastroplication with the ACE stapler affects food intake, hunger and fullness and the release of the gut-derived peptides ghrelin, GLP-1 and PYY. These results provide insight in the mechanisms of action of this new minimal invasive procedure.

Signals originating from the gastrointestinal tract are crucial for the regulation of food intake and satiation. The presence of food in the stomach and small intestine induces the release of several satiety signals, either by distension of the stomach or by stimulation of intestinal chemosensory receptors. In contrast to intestinal satiation, which is merely nutritive, gastric satiation is known to be volume dependent (20). Several studies have shown that gastric mechanosensation plays an important role in the regulation of food intake (21, 22). Under physiological conditions ingestion of a meal results in pressure and volume changes in the stomach, influencing satiation and meal size via vagal efferents (23). In this study, multiple plications in the proximal stomach were created in order to reduce gastric volume. We found that this not only resulted in a decrease in hunger and increase in fullness but also in a fifty per cent decrease in ad libitum food intake 1 month postoperatively. We hypothesize that plicating the stomach induces accelerated and increased gastric stretch, from which is known that it can play an important role in the regulation of food intake (20-22, 24). Furthermore, a similar increase in postprandial fullness is seen after laparoscopic fundoplication; in which volume reduction of the proximal stomach is also established (25). Comparable results with regard to satiety and food intake were seen after temporary placement of a 400mL intragastric balloon (26).

The stomach-derived orexigenic hormone ghrelin is known to be an important mediator in promoting a positive energy balance by stimulating food intake. Ghrelin secretion is controlled via efferent vagal branches that stimulate the enteroendocrine cells of the stomach to secrete ghrelin in the fasted state and inhibit ghrelin secretion postprandial (27). In the current study we found an increase in fasted ghrelin levels post procedural, confirming previous literature findings on the weight loss associated effects on fasted ghrelin after LAGB (12, 28, 29).

Ghrelin level is associated with nutritional status: it increases after a period of fasting and rapidly decreases after food intake (30). In the current study, this food induced ghrelin decrease was observed only after gastroplication and not before the procedure. It is suggestible that ingestion of our relatively small breakfast caused significant tension on mechanosensitive receptors of the plicated stomach, while the volume of the breakfast was too small to cause a similar response in the larger, unpli-

cated stomach. However, in a study in rats, gastric distention was insufficient in eliciting the postprandial ghrelin decrease, so this mechanism may not be held solely responsible for the decrease in ghrelin levels (31). On the other hand, Mion et al. showed that gastric distention through placement of a gastric balloon resulted in a decrease in fasted ghrelin levels, despite significant weight loss (32). Therefore, they proposed a mechanism whereby fundic distention can inhibit ghrelin secretion. Overall, further human studies are needed to fully elucidate these mechanisms.

In contrast to the stomach, the small intestine provides feedback based on nutritive content, rather than volume (20). Satiety increases when nutrients reach the small intestine, partly mediated by anorexigenic hormones like PYY and GLP-1.

We observed a weight loss induced decrease in the fasted levels of PYY and GLP-1 one month after the procedure compared to baseline, as was shown in a recent study by Sumithran et al. This blunted response of the small intestine to nutrients suggests a compensatory hormone response, to stimulate food intake and regain stable body weight. However, while this decrease persists up to one year after diet-induced weight loss (33), an increase is observed one year after ACE stapling. This could mean that a new 'set-point' has been established within twelve months, providing a stronger satiating signal and possibly aiding in stable or even continued weight loss, as has been found after LAGB. However, in that study the effect did not persist up to 52 weeks (12).

Gastric emptying (GE) rate after bariatric surgery has been extensively studied and seems to be related to the type of surgery performed (34, 35). Other restrictive procedures are expected to be most comparable to gastroplication. LAGB did not alter overall GE rate, (8, 36) while both increased and decreased GE rates have been observed after laparoscopic sleeve gastrectomy (9, 37, 38). Our data are in agreement with the previously mentioned LAGB data since we could not find changes in gastric emptying after gastroplication. In our study most of the plications were created in the fundus of the stomach while only two plications were created in the antral region. An intact antral region seems to be of importance for normal gastric emptying (9). We can only speculate that the antrum and fundus are insufficiently altered to influence GE rate, or that the proximal and distal plications counteract each other's effects.

Strength of this study is the prospective, standardized design of all follow-up moments and test days. We extensively studied the effects at 1 and 12 months post-procedural compared to baseline, without experiencing any loss to follow-up. Although this exploratory phase 1 study was performed in a small group of patients we were able to find statistically significant and physiologically relevant changes. However, some of our data need to be interpreted with caution, since we found a significant increase in hunger and ad libitum food intake 12 months after the procedure compared to 1 month, suggesting a possible loss of effect on hunger and ad libitum food intake.

Chronic overeating may induce stretch on the stomach wall leading to dilation of the proximal stomach and possible reversal of the effect, similar to dilation of the gastric pouch in RYGB (39). Extending follow-up duration could elucidate on the extent of this reversal. For future studies it would also be advisable to add a control group to gain strength and to further differentiate between the effects of weight loss and the procedure itself.

In conclusion, the reduction of ad libitum food intake and the decrease in hunger feelings partially paralleled by changes in the gut-derived peptides support the effects of endoscopic gastric plication with the ACE stapler. Gastric emptying rate was unaltered, suggesting that this cannot be seen as an important mediator of gastroplication-induced weight loss. With this prospective study we give new insights in the mechanism of action of endoscopic gastric plication, which guides future research and development of the technique.

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Effect of Endoscopic Gastroplication on the Genome-Wide Transcriptome in the Upper Gastrointestinal Tract

ABSTRACT

BACKGROUND

Bariatric surgery is an effective intervention strategy in obesity, resulting in sustained weight loss and a reduction of comorbidities. Gastroplication, using the articulating circular endoscopic stapler, was recently introduced as a transoral bariatric technique. This procedure reduces gastric volume and induced 34.9% of excess weight loss in the first year (Paulus et al. Gastrointest Endosc. 81(2):312–20, 3). The aim of the present study was to gain insight in the long-term effects and underlying mechanisms of gastroplication by investigating differences in the genome-wide gastric and duodenal transcriptome before and 1 year after intervention.

METHODS

Ten morbidly obese patients (BMI 39.8 ± 0.9 kg/m² (mean ± SEM)) underwent gastroplication. Previous to the procedure and after 1 year, blood samples were taken, and mucosal biopsies were collected from the fundus, antrum and duodenum. Gene expression was measured using microarray analysis. Plasma

adiponectin, HbA1c, IL-1ß, IL- 6, IL-7, TNF-α, IFN-γ, MCP-1, IL-8, TGF-1 and CRP levels were determined.

RESULTS

Downregulation of inflammatory genes and gene sets was observed in the fundus and duodenum 1 year after surgery. Gene expression of ghrelin and its activating enzyme GOAT were downregulated in the upper gastrointestinal tract. Patients showed a reduction in plasma HbA1c levels (from 6.17 ± 0.51 to 5.32 ± 0.14 %, p=0.004) and an increase of plasma adiponectin (from 16.87 ± 3.67 to 27.67 ± 5.92 µg/ml, p=0.002).

CONCLUSIONS

Individuals undergoing gastroplication displayed a downregulation of inflammatory tone in the stomach and duodenum, which coincided with improved HbA1c and adiponectin levels. The reduction of inflammatory tone in the upper gastrointestinal tract may be a consequence of an improved metabolic health status or alternatively caused by the procedure itself.

INTRODUCTION

Bariatric surgery is the most effective medical option to achieve sustained weight loss in severe obesity. Besides traditional procedures such as laparoscopic Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG) and adjustable gastric banding (LAGB), less invasive options are available such as the (transorally placed) duodenal-jejunal bypass sleeve (DJBS). In general, these procedures lead to a loss of body fat, a reduction of comorbidities and improvement of long-term health risks. Remarkably, the mechanisms behind these outcomes are still poorly understood, and it is conceivable that these comprise different combinations of biological adaptations (1). This is reflected in the markedly different immediate effects on glycaemic control following different procedures (2). Recently, endoscopic gastroplication has become available as a new minimal invasive technique. The articulating circular endoscopic (ACE) stapler is used to reduce the volume of the stomach without removing tissue or bypassing other intestinal regions. For this procedure, no skin incisions are necessary; it is performed via a transoral route. This procedure results in a median 34.9% (IQR 17.8–46.6) loss of excess weight in the first year. Moreover, only mild adverse effects were reported so far (3). Although several studies have described metabolic and anti-inflammatoreffects of bariatric surgery at a molecular level, studies on these processes within the gastrointestinal (GI) tract are still limited. This holds particularly true for the upper GI tract, as most studies in this field have focussed on the mid or lower gastrointestinal tract (4–6). Moreover, these studies concern effects of RYGB, a procedure extensively changing GI anatomy and physiology. The present study was undertaken to gain more insight in the long-term effects and underlying mechanisms of gastroplication in the upper GI tract: the stomach (fundus and antrum) and the duodenum, and to relate these to general health outcomes, including parameters of inflammation. To this end, transcriptome and gene set enrichment analysis was performed with biopsies obtained before and 1 year following gastroplication.

MATERIALS AND METHODS

ACE stapler study

This study used biopsies and blood samples obtained from ten patients who were part of the first human ACE stapler study (3). The Medical Ethical Committee of the Maastricht University Medical Center+ in the Netherlands (NCT02381340) approved the present study as a sub-study aiming to further unravel underlying mechanisms. Before inclusion, written informed consent was obtained from each participant. The inclusion criteria for the ACE stapler study are described in detail by Paulus et al. (3). In brief, participants were 18 to 50 years old with a BMI of 40 to 45 kg/m² or 30 to 39.9 kg/m² in combination with one or more comorbidities expected to improve with weight loss. The ACE stapler was introduced into the stomach together with a thin endoscope. By applying vacuum to the gastric tissue, a large full-thickness (transmural) plication was drawn into the stapler head and fixed with a staple ring. Reduction of the stomach volume along the greater curvature was completed after creating a maximum of eight plications in the fundus and two additional plications in the antrum of the stomach. More details on the procedure were published previously (3). Mucosal biopsies were taken from the fundus, antrum and duodenum with a standard forceps before starting the procedure. Afterwards, patients visited the outpatient clinic regularly and were stimulated to adhere to a healthy lifestyle. A follow-up endoscopy was planned 12 months after the procedure, at which the biopsy procedure was repeated. Biopsies were snap frozen in liquid nitrogen and stored at –80 °C until analysis. Table 7.1 shows a brief overview of the characteristics of included patients.

	Baseline		One year	
	Mean	SEM	Mean	SEM
Age	39	2		
Male:Female ratio	6:4			
BMI (kg/m²)	39.8	0.9	33.4	0.9
Excess weight loss (%)			37.9	4.8
Fasted active ghrelin level (pg/ml)	46.5	5.9	63.4	5.2

Table 7.1 | *Overview of characteristics of patients undergoing ACE stapler procedure. Measurements were performed at baseline and 1 year after the procedure. Ghrelin was measured after a 10 hour overnight fast.*

RNA isolation and microarray processing

RNA of the mucosal biopsies was isolated using TRIzol reagent (Life technologies, Bleiswijk, Netherlands) and further purified using the RNeasy micro kit (Qiagen, Venlo, Netherlands). RNA yield was measured with the Nanodrop ND-1000 Spectrophotometer, and the quality of the RNA samples was verified with an Agilent 2100 Bio analyser (Agilent Technologies, Amstelveen, Netherlands). One hundred nanogram of RNA was used for whole transcript cDNA synthesis (Affymetrix, Inc., Santa Clara, USA). Hybridization, washing and scanning of Affymetrix GeneChip Human Gene 1.1 ST arrays was carried out according to standard Affymetrix protocols.

Microarray analysis

For the analysis of the microarray results, each location (i.e. fundus, antrum and duodenum) was analysed separately. Arrays were normalized using the robust multiarray average method (7, 8). Probe sets were assigned to unique gene identifiers, in this case Entrez IDs. The probes on the arrays represent 19654 Entrez IDs (9). Array data were analysed using MADMAX pipeline for statistical analysis of microarray data (10). Quality control was performed, and all arrays met our criteria, except for the fundus and antrum arrays from participant 5, which were excluded. All data were filtered, and probe sets with expression values above 20 in at least 5 arrays were included for further analysis. These data were used for gene set enrichment analysis (GSEA; www.broadinstitute. org/gsea (11)) in MADMAX. Gene sets with a false discovery rate (FDR) <0.25 were considered significantly enriched. The gene set enrichment analysis was visualized using the enrichment plugin in Cytoscape with conservative filtering ($p < 0.001$ and FDR $q < 0.05$). For further analysis of individual genes, a cut-off of IQR > 0.25 was used to filter out genes that showed no variation between the samples; Intensity-Based Moderated T-statistics (IBMT) was used to assess significant differences with p value <0.05.

Plasma measurements

Blood samples were collected in EDTA-coated tubes, centrifuged and stored at −80 °C until analysis. The measurement of plasma adiponectin and cytokine levels was performed using an in-house developed and validated multiplex immunoassay (Laboratory of Translational Immunology, University Medical Center Utrecht, the Netherlands) based on Luminex technology (xMAP, Luminex, Austin, USA). The assay was performed as described previously (12). Using heteroblock (Omega Biologicals, Bozeman, USA), aspecific heterophilic immunoglobulins were preabsorbed. Acquisi-

tion was performed with the Biorad FlexMAP3D (Biorad laboratories, Hercules, USA) in combination with xPONENT software version 4.2 (Luminex, Austin, USA). Data was analysed by 5-parametric curve fitting using Bio-Plex Manager software, version 6.1.1 (Biorad laboratories, Hercules, USA). HbA1c levels were determined routinely at the Department of Clinical Chemistry of the Maastricht University Medical Center. Active ghrelin was measured using an established in-house radioimmunoassay (Millipore, Massachusetts, USA).

Statistical analysis

Statistical analyses were performed using Prism 5.0 (GraphPad Software, Inc. La Jolla, USA). The effects of treatment on plasma levels of inflammatory markers and adiponectin were tested by paired t tests for normally distributed variables and Wilcoxon's signed rank tests for non-normally distributed variables. Spearman's rank correlation coefficient analysis was performed to investigate the association between changes in biochemical parameters with changes in mRNA expression (signal log ratio). A p value <0.05 was considered statistically significant. Data are presented as mean with standard error of the mean (SEM). Statistical analysis of transcriptome data was described above.

RESULTS

Effects of gastroplication on systemic metabolic and inflammatory parameters one year after intervention

Plasma levels of glycated haemoglobin, adiponectin and several pro-inflammatory mediators before and after intervention are shown in Table 7.2. Significant changes were found for adiponectin and HbA1c. Adiponectin showed a 1.64-fold increase ($p=0.002$) in the patients who underwent ACE stapler treatment. Glycated haemoglobin (HbA1c) was significantly decreased ($p=0.004$) by the treatment. Plasma IL-6 showed a tendency to decrease following ACE stapler treatment by a factor 1.47. MCP- 1 levels also showed a decrease (1.3-fold), but this effect did not reach statistical significance.

Plasma marker		Baseline		One year		Treatment effect	
	Unit	Mean	SEM	Mean	SEM	Difference	p-value
Adiponectin	µg/ml	16.87	3.67	27.67	5.92	10.80	0.002*
HbA1c	%	6.17	0.51	5.32	0.14	-0.85	0.004*
IL-1ß	pg/ml	1.42	0.06	1.37	0.08	-0.05	0.244
IL-6	pg/ml	10.90	1.83	7.41	1.80	-3.49	0.069
IL-7	pg/ml	11.52	1.24	10.43	2.01	-1.09	0.180
TNF-α	pg/ml	2.14	0.10	2.00	0.14	-0.14	0.118
IFN-γ	pg/ml	2.54	0.27	2.23	0.25	-0.32	0.099
MCP-1	pg/ml	60.70	7.33	46.68	7.74	-14.02	0.088
IL-8	pg/ml	7.03	1.03	6.55	1.44	-0.48	0.455
LAP / TGF-1	ng/ml	3.11	0.35	3.24	0.36	0.13	0.393
CRP	mg/l	12.62	5.66	8.78	2.75	-3.85	0.248

Table 7.2 | *The effect of ACE stapler treatment on fasted plasma levels of inflammatory and metabolic markers. Plasma levels were measured before the treatment (baseline) and 1 year after.*

Effects on tissue gene expression mainly relate to inflammatory pathways

Gene expression changes 1 year after intervention compared to baseline were analysed for different locations of the upper gastrointestinal tract, namely fundus, antrum and duodenum. After intervention, 727 genes (259 upregulated, 468 downregulated) were significantly changed in the fundus, 1846 (951 upregulated, 895 downregulated) in the antrum and 921 genes (480 upregulated, 441 downregulated) in the duodenum. The top 20 upregulated and downregulated genes in all three locations are shown in Figure 7.1. In both fundus and duodenum, a considerable number of downregulated genes have been associated with immunity and inflammatory pathways. In the fundus, the expression of immune-related genes like IGHV3-33, C7, CCL21, IFI6, IFI27, C1QB was downregulated, and CCL18, CLC, CXCR4, IGHV1-24, RSG1, IGLV3-10, IGHV3-33, IGLV7-46 were downregulated in the duodenum. In the antrum, there was an upregulation of some neuroendocrine-associated genes, namely PAX6, CHGB, SCG5.

Gene set enrichment analysis reveals potential processes involved

To gain more insight into the processes changed 1 year following the stomach volume reduction procedure, gene set enrichment analysis (GSEA) was performed. This computational method uses molecular signatures to associate changes in gene expression

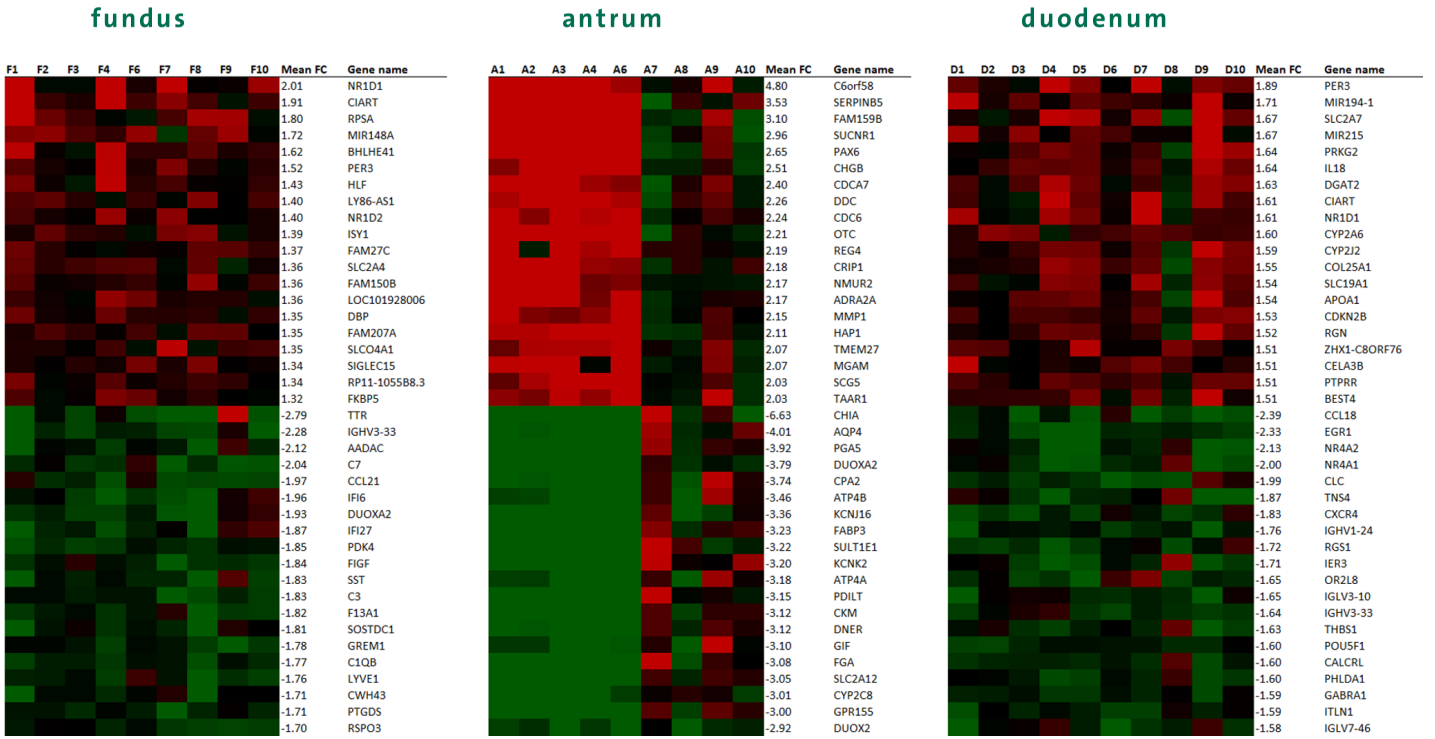


Figure 7.1 | *Expression of most highly significantly upregulated and downregulated genes in fundus, antrum and duodenum, respectively. Green is a signal log ratio of –2, and red is a signal log ratio of 2. Apart from the mean fold change (FC) of the top regulated genes by the treatment, signal log ratios are displayed to show inter-individual differences*

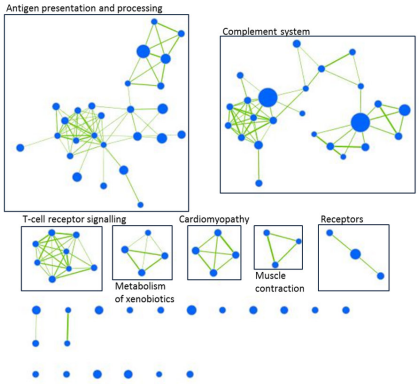
with known biological processes. Analysis resulted in 236 (2 upregulated, 234 downregulated) enriched gene sets for fundus, 546 (474 upregulated, 72 downregulated) enriched gene sets for antrum and 253 (182 upregulated, 71 downregulated) enriched gene sets for duodenum. In the antrum, more gene sets were upregulated, whereas in the fundus, most gene sets were downregulated (Figure 7.2). Of these downregulated gene sets in the fundus, many were related to immune responses, mostly to the complement system, presentation and recognition of antigens (self or pathogenic) and T cell receptor signalling. Also in the duodenum, some of the downregulated gene sets were related to the innate immunity. In the antrum, cell cycle related gene sets were strongly enriched. In the duodenum, the enrichment analysis showed also a slight upregulation of cell cycle processes. Here, more metabolic pathways were apparently upregulated, including those associated with 'fat digestion and absorption' and 'metabolism of lipids and lipoproteins'. All gene sets are specified in Table S1 (online supplement).

Changes in gastrointestinal hormone expression

Being one of the main gastric hormones, ghrelin is not only involved in appetite regulation but also in immunity (13). Two genes related to ghrelin were significantly changed in specific locations of the GI tract (Figure 7.3a). In the fundus, there was a downregulation of MBOAT4 (FC=–1.49), the gene encoding the ghrelin-activating enzyme GOAT4. Furthermore, there was a trend for downregulation of ghrelin (GHRL) expression itself in the fundus (FC=–1.88, p=0.19) and antrum (FC=–3.13, p=0.11) and a significant downregulation in the duodenum (FC=–1.34). In the fundus, the ghrelin gene expression (GHRL) was positively correlated to fasted plasma changes of active ghrelin (Spearman correlation coefficient = 0.826, p=0.015), and for MBOAT4 expression, there was a tendency for correlation (Spearman correlation coefficient = 0.69, p=0.069) (Figure 7.3b). Although the correlation between changes in ghrelin and GHRL expression seems to be influenced by a single patient, excluding this patient still resulted in a significant correlation.

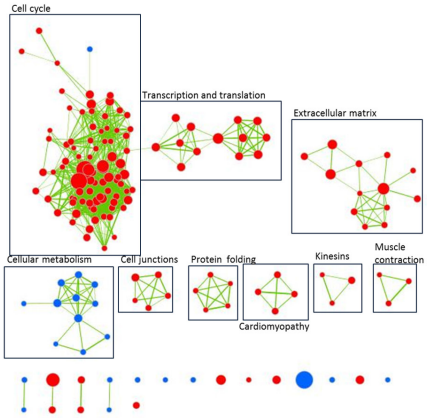
A

Fundus



B

Antrum



C

Duodenum

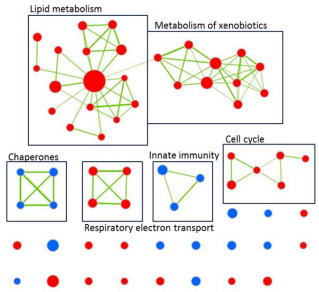


Figure 7.2 | *Gene set enrichment analysis of the fundus, antrum and duodenum. Each node indicates a conservative filtered gene set (p < 0.001 and FDR q < 0.05), and the connecting lines indicate overlapping genes between the nodes/gene sets. Red is enriched; blue is depleted gene sets.*

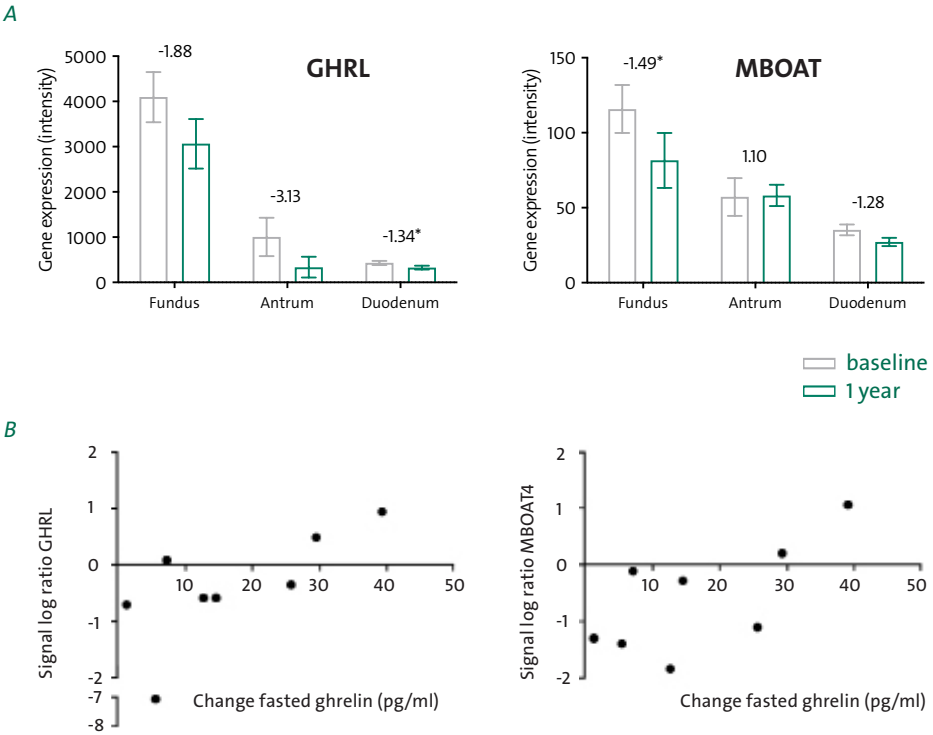


Figure 7.3 | *Changes in gene expression of ghrelin and MBOAT4 and their correlation to plasma ghrelin. a) The graphs show RMA normalized intensities of microarray data at baseline and 1 year after gastroplication in biopsies of fundus, antrum and duodenum. Fold changes are indicated on top of the bars, significant changes are marked with asterisk (p < 0.05). All graphs show mean and SEM. b) Correlation between signal log ratios of ghrelin (GHRL) and MBOAT4 in the fundus with changes in plasma active ghrelin levels measured in a fasted state before and 1 year after the procedure.*

CONCLUSIONS

Results of the present study add important physiological background information to the clinical outcomes observed in patients after undergoing ACE stapler gastroplication. Our plasma analyses revealed beneficial effects on HbA1c and adiponectin levels 1 year after surgery, indicating an improvement of glycaemic control and a favourable shift in adipose tissue mass and/or inflammatory status, respectively. This rise in plasma adiponectin and reduction of HbA1c is in line with previous studies in which a loss of excess body fat was achieved, including those involving other surgical and non-surgical weight loss interventions (14–17). We also found tendencies for reduced plasma IL-6 and MCP-1 levels, 1 year after intervention. Reduced levels of inflammatory markers are generally assumed to result from a reduction of visceral fat mass in particular, which plays a major role in the low grade inflammatory state associated with obesity (18). The total number of patients in our study population is quite small, and it is conceivable that statistical significance might have been reached with a larger patient group. Several other studies have found significant reductions in inflammatory markers like CRP, MCP-1 and IL-6 after bariatric surgery, while others did not find such an effect (19–21).

To our knowledge, this study is the first to analyse longterm whole transcriptome changes in the upper gastrointestinal tract after a new transoral bariatric procedure. Gastroplication reduces gastric volume without altering intestinal anatomy, as is the case with RYGB. In contrast to bypass surgery, exposure of the intestinal epithelium to nutrients and their metabolites is largely maintained after this endoscopic gastroplication. At the same time, small changes related to different GI transit characteristics or changes in the microbiome might still occur.

Analysis of the large amount of data using unbiased transcriptome analysis clearly pointed towards a reduction in inflammatory tone in the fundus and duodenum tissues as manifested by the downregulation of a wide variety of inflammation-related gene sets. The downregulated gene sets in the fundus were mostly related to innate immunity, and particularly associated with downregulation of the complement system, presentation and recognition of antigens (self or pathogenic), IFN-γ signalling and T cell receptor signalling. In the duodenum, the main downregulated gene set was associated with the complement system. Moreover, the top 20 highly changed genes in these locations also suggest notable downregulation of many immune-related processes, of which several were related to chemokines, complement system, interferon signalling and immunoglobulins. These results coincided with the weight loss, improvement of HbA1c levels and decrease of whole-body inflammatory tone in these patients.

Based on the present study, we cannot establish whether the apparent reduction of inflammatory tone in the upper GI tract has a predominantly local cause, i.e. due to a changed food intake pattern or digestion process, or whether it is related to a reduction of low-grade systemic inflammation due to the reduction of body fat mass.

Increasing evidence points to a link between intestinal inflammation status in general, obesity and (or) diabetes. In obesity, increased innate cell densities, among which macrophages, natural killer cells and T cells, especially the proportion of cytotoxic CD8 T cells, have been observed in the jejunal epithelium. These epithelial T cells were found to be associated with local and systemic comorbidities. Furthermore, isolated T cells from obese patients decreased insulin sensitivity of epithelial cells in vitro (22). Another study reported that diet-induced weight loss resulted in a downregulation of inflammatory pathways and inflammatory cytokines IL-8, TNF-α, MCP-1 and IL-1ß, in recto-sigmoid mucosal tissue (23). Moreover, increased intestinal inflammatory gene expression of TNF-α, IL-6, ICAM and PTGS-2 was found in insulin-resistant obese patients compared to noninsulin- resistant obese patients, suggesting that intestinal inflammation is involved in diabetes during obesity (24, 25). A prominent feature of the immune system in the gastrointestinal tract is to provide adequate protection without stimulating excessive inflammation, thereby maintaining a fine balance (26, 27). A pro-inflammatory immune status of the gastrointestinal tract in obese patients might be protective against increased luminal challenges associated within obesity but deteriorating for insulin resistance (22). Furthermore, this proinflammatory status might be linked to the increased prevalence of inflammatory bowel disease and cancer in obese patients (28–30). In summary, we can only speculate whether the reduced inflammatory microenvironment in gastric and duodenal tissue found after gastroplication can be considered as a positive or negative outcome.

In the antral tissue, gene sets related to cell cycle processes and extracellular matrix were increased. This might be explained by dilation of the stomach, a common observation after gastric volume reduction (31–34). While gastric volume was not quantified, we perceived the stomach as larger at 1-year follow-up than immediately after gastroplication.

An interesting observation was that the mean gene expression of ghrelin and the enzyme GOAT, responsible for ghrelin acylation, decreased after gastroplication in some of the tissues. At the same time, plasma fasted active ghrelin was increased, and there was a positive correlation between the gene expression of ghrelin and plasma values of active ghrelin. Ghrelin is one of the most prominent hormones secreted from the upper gastrointestinal tract and does not only play a role in appetite regulation but also in inflammation (13). Consistent with our results, in RYGB patients, significant lower levels of jejunal ghrelin gene expression have been reported after 10 months (6).

Furthermore, GOAT mRNA expression and GOAT positive cell numbers were lower in a non-obese group compared to morbidly obese patients, although no changes in jejunal ghrelin expression were detected (35). Moreover, more ghrelin positive cells were found in the stomach of morbidly obese and overweight patients compared to healthy normal weight controls (36, 37), which might indicate that with weight loss, the number of ghrelin-releasing cells will decrease. The discrepancy with ghrelin expression in the gastrointestinal tract and plasma ghrelin values might be explained by a reduced secretory activity of (a higher number of) ghrelin producing cells in obesity, as suggested by Widmayer et al. (36). However, within our patients, there was a positive correlation between its gene expression and plasma levels, indicating that upregulated expression of ghrelin in the fundus was associated with greater increase in fasted ghrelin levels and downregulated expression with a smaller increase 1 year after gastroplication. The underlying cause of the observed changes cannot be pinpointed in our study. It is possible that the changes in ghrelin are dependent on the surgical procedure, which takes place at the main site of ghrelin secretion. Furthermore, the implications of these changes in ghrelin are not fully understood and need further investigation to crystallize the underlying mechanism and to explore the potential of these changes in obesity treatment.

There are some strengths and limitations to this study. The within-person measurement of changes in gastrointestinal gene expression is unique as most studies in this field are observational. By applying a prospective design, we were able to perform paired analysis and look specifically for changes induced by the gastroplication treatment instead of comparing obese subjects with lean controls. Whole transcriptome analysis enabled us to investigate changes in an unbiased manner. One of the limitations of this study is that it was not powered to find differences in inflammatory markers. Therefore, the inclusion of more patients could have strengthened the study. Furthermore, a control group on a lifestyle intervention program could help differentiate between weight loss effects and strictly procedural effects.

This study presents the long-term effects of a new transoral gastroplication treatment in morbidly obese patients. We show that this recently developed ACE stapler procedure was not only effective in reducing body weight as presented before (3), but also improved glycated haemoglobin levels and increased plasma adiponectin. Furthermore, whole transcriptome analysis suggested a marked downregulation of inflammatory gene sets in both the fundus and duodenum, coinciding with changes in plasma cytokines. Moreover, gene expression of ghrelin and its activating enzyme GOAT were reduced after gastroplication. The apparent reduction of inflammatory tone in the upper GI tract may be a consequence of an improved metabolic health status as associated with weight loss, or alternatively caused by the procedure itself.

In conclusion, this new transoral gastroplication treatment which induced significant weight loss and improved plasma levels of adiponectin and glycated haemoglobin coincides with a reduced inflammatory tone in the upper GI tract. The clinical relevance of our findings remains to be established, as there is still limited knowledge on the role of inflammatory pathways in the upper GI tract in obesity.

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Preliminary Evidence that Endoscopic Gastroplication Reduces Food Reward

ABSTRACT

Morbidly obese patients are most successfully treated with bariatric surgery. Although restrictive gastric surgery physically limits food intake, it is also suggested that eating behavior and food-reward mechanisms are affected. Therefore, eating behavior and food-reward were assessed in ten patients that underwent gastric volume reduction by endoscopic gastroplication. Patients participated in test days before and one, three and twelve months after the procedure. Weight loss, food intake, appetite, gastric emptying rate, food-reward (i.e. liking and wanting) and eating behavior were assessed. Body mass index decreased from 38.3 (37.6–42.6) to 33.9 (31.0–35.9) kg/m² after one year. Ad libitum food intake decreased significantly after one month, but not after one year. Gastric emptying rate did not change. AUC of VAS scores for desire to eat, quantity, fullness, hunger, snacking and satiety changed after

one month, but not all remained significantly changed after one year. Thirst did not change. Liking scores of food items decreased significantly in the fasted as well as the satiated state after the procedure. Wanting scores did not change. Uncontrolled eating decreased significantly after three and twelve months; emotional eating was only significantly decreased after three months. The results show that food intake decreases, while VAS scores for appetite and eating behavior change accordingly. Liking, but not wanting of food items changed to benefit the weight losing patient. The effects were stronger at one-month follow-up than at 12 months, which may be a risk of relapse after initial successful weight loss. The effects of new bariatric procedures on food-reward should be studied in future randomized trials to further elucidate their impact.

INTRODUCTION

Morbid obesity is a worldwide epidemic that is increasingly being treated by bariatric surgery. Most common procedures such as sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) are performed laparoscopically, but still carry a considerable risk of complications (1,2). New endoluminal approaches like endoscopic gastroplication aim to reduce both recovery time and complication rates. A recently studied gastroplication technique with the Articulating Circular Endoscopic (ACE) stapler (Boston Scientific Corporation, Marlborough, Massachusetts), showed promising weight loss results with an excellent safety profile in an experimental multicenter setting. In brief, the technique is performed as follows. The ACE stapler has a silicone cap, which uses vacuum to acquire tissue and place it between the stapler arms. The stapler is inserted to the stomach together with an endoscope through the esophagus, after which up to ten full-thickness plications are created in the fundus and antrum. Aim of the procedure is to induce volume restriction, without the need of a laparoscopic approach. The technique is described in detail in the original paper (3).

While diets and lifestyle programs are often inefficient in the longer term, bariatric surgery without lifestyle adaptation also carries risk of relapse after initial successful weight loss. The reason why some people overeat and become morbidly obese is usually multi-causal. Feeding is controlled by both homeostatic hunger and hedonic hunger: 'the drive to eat to obtain pleasure in the absence of an energy deficit'. One aspect of hedonic hunger mechanisms is food reward, which can be expressed in terms of 'liking' and 'wanting' of food. Studies have shown that subjects with obesity, have a greater motivation to obtain and consume food, corrected for energy requirement, especially during stress (4-9).

Bariatric procedures alter the anatomy of the gastrointestinal tract and were initially developed to cause physical restriction of the amount of intake and/or to induce malabsorption by altering the pathway through the digestive tract. However, it is now clear that bariatric procedures result in weight loss and metabolic improvement by other mechanisms than restriction or malabsorption alone. Reduced energy intake, as a result of altered eating behavior, is the main driver for weight loss in humans following RYGB and LSG. The biological mediators underlying altered eating behavior are not yet fully understood, but altered responses of gut hormones, bile acid and microbiome are key candidates (10-12). Food reward was investigated before by other authors after laparoscopic adjustable gastric banding, LSG and RYGB using functional MRI (fMRI), eye-tracking or computer tasks and found significant changes (13-16).
The aim of this pilot study was to evaluate changes in eating behavior and food reward

after gastroplication in ten patients who were available from a safety and feasibility study on effectiveness of endoscopic gastroplication with the ACE stapler.

SUBJECTS AND METHODS

Subjects

A subset of patients from a multicenter trial (for subject characteristics see Table 8.1) to evaluate the safety and preliminary effectiveness of endoscopic gastroplication with the ACE stapler was studied. We included all ten patients who were treated in our hospital, who gave separate written informed consent for this sub study. Parameters used to express weight loss are body weight, body mass index (BMI) and excess weight loss (EWL). Excess weight was defined as the excess to a BMI of 25 kg/m². The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center (July 5, 2012, ClinicalTrials.gov: NCT02381340).

Appetite and ad libitum food intake

Subjects visited our facility for a test day before the procedure (baseline, BL) and returned one month (1M) and one year (12M) after gastroplication. Test days were identical and started after a 10-h fast at 8.30 a.m. with the collection of several appetite scores and breath samples for the evaluation of gastric emptying rate. A standardized breakfast meal, consisting of a sandwich with an egg (sunny side up, 879 kJ) and 250 mL water, was consumed before collection of appetite scores and breath samples was

	baseline		one month			twelve months		
	median	IQR	median	IQR	p	median	IQR	p
Age (y)	37	32 – 49.8						
Gender (m/f)	6/4							
BMI (kg/m²)	38.3	37.6 – 42.6	35.6	35.1 – 39.6	0.002*	33.9	31.0 – 35.9	0.002*
EWL (%)	-	-	14.4	11.8 – 19.8	0.002*	38.0	28.1 – 45.6	0.002*
Body weight (kg)	119.1	114.9 – 129.5	111.6	106.8 – 120.4	0.002*	101.4	98.0 – 106.1	0.002*

Table 8.1 | *Baseline characteristics and weight evolution. Data are expressed as median (IQR: 25th-75th percentile). * statistically significant difference compared to baseline (Friedman p<0.05 and Wilcoxon post-hoc p<0.025).*

repeated at regular intervals during the next 270 min. An ad libitum pasta meal (Lasagna Bolognese; energy density per 100 g: 669 kJ; 7.1 g protein, 11.0 g carbohydrates and 9.4 g fat) was provided 240 min after breakfast.

Scores for appetite were measured using visual analogue scales (VAS; 0–100 mm), anchored at the low end with the lowest intensity feelings ('not at all'), and with opposing terms at the high end ('extremely'). The VAS questionnaire included desire to eat (How strong is your desire to eat?), quantity (How much would you like to eat?), prospective snacking (How strong is your desire to snack?), thirst (How thirsty are you?) and satiety or fullness (How satiated or how full are you?) (17,18).

Gastric emptying rate was determined using the 13C stable isotope breath test. 13C-octanoic acid (100 mg, Campro Scientific bv, Veenendaal, the Netherlands) was injected into the egg yolk during preparation of the breakfast. Breath samples of $^{13}CO_2$ were obtained and analyzed as described previously by using Isotope Ratio Mass Spectometry (IRIS, Wagner, Bremen, Germany) (19).

Food reward

Food reward was measured before and after the ad libitum lunch meal, 4 h after the standardized breakfast. A validated computer test was used to measure the rewarding value (i.e. "liking" and "wanting") of 72 items in six twelve-item categories: bread, (sandwich) fillings, drinks, dessert, sweets and as a control, stationary (non-food). The 72 items were presented as photographic stimuli on a computer screen (13- inch Mac Book; Apple, Cupertino, CA) (20).

Subjects indicated their relative preference of food items within and between categories during the "liking" part of the computer test, resulting in a scoring of the items per category. During the "wanting" part of the computer test, subjects had to work to earn items to choose from by playing a memory game. For each category subjects played a memory game with 12 pairs of items, followed by indicating the items patients wanted to acquire and, in the case of food-items, eat at that moment. The number of items that could be chosen from was equal to the number of pairs found in the memory game, representing the motivation or workload for the chosen items. Patients were allowed to choose zero, one or two items per category and were instructed to choose as if the items would have to be consumed completely after the test was finished (except for stationary items). Per category the "wanting" score was calculated by multiplying the number of pairs found by the number of chosen items. (5, 6, 17, 20). Wanting and liking scores of food items were corrected for the control score (stationary).

Eating behavior

Eating behavior was assessed at baseline, at a 3-month follow-up visit and at the one-year test day with the TFEQ-R18 (three factor eating questionnaire) and the EDE-Q (eating disorder examination questionnaire).

The TFEQ-R18 is an 18-item questionnaire on three different aspects of eating behavior: cognitive restraint (the tendency to constantly and consciously restrict food intake instead of using physiological cues, like hunger and satiety, as regulators), uncontrolled eating (the tendency to overeat, with the feeling of being out of control) and emotional eating (the tendency to eat in response to negative emotions) (21-23). The raw scores (1–4 or 1–8) were converted to a 0–100 scale. Higher scores indicate greater cognitive restraint, uncontrolled eating or emotional eating.

The EDE-Q is a 36-item questionnaire on eating disorder psychopathology. It focuses on the previous 28 days and contains several subscales: restraint eating, eating concern, weight concern and shape concern. Items are scored on a 7-point Likert-scale (0–6) and for subscale scores; the items belonging to a certain subscale were averaged. A higher score indicates greater severity of eating disorder psychopathology (24).

Statistical analyses

There was no loss to follow-up. In case of missing data, the patient was excluded for that particular analysis. Because of the small sample size, a Gaussian distribution of all outcomes could not be assessed. Therefore, data are presented as the median with 25th and 75th percentiles (interquartile range, IQR) and tested using non-parametric tests. Friedman's ANOVA was used for multiple comparisons, with Wilcoxon signed rank-test as post hoc analysis. For post-hoc analysis a Bonferroni correction was applied to correct for multiple comparisons (BL vs 1M and BL vs 12M). Therefore, a p-value < 0.025 was regarded statistically significant. The wanting and liking data are compiled of many samples per test. A Gaussian distribution was confirmed by D'Agostino-Pearson omnibus K2 test for normality ($P > 0.05$) and therefore repeated measures ANOVA was used, with Tukey's multiple comparisons test for post-hoc analysis. These data are presented as mean + standard error of the mean (SEM). Total VAS scores were expressed as area under the curve (AUC) from t=0 to t=240. The relation between excess weight loss and change in TFEQ or change in total VAS scores was tested with Pearson's test for correlation.

Statistical analyses were performed and graphs were created using SPSS 21.0 (IBM Corporation, Somers, NY) and Prism 8.0 (GraphPad Software, Inc. La Jolla, CA).

RESULTS

Subjects

Baseline characteristics and weight evolution are presented in Table 8.1. Ten subjects (100% of patients who were treated in our hospital) were included in this study between July and November 2012.

Ad-libitum food intake was decreased at one month after the procedure compared to baseline, while the decrease at 12 months did not reach statistical significance (p=0.037). Gastric-emptying half time was not influenced by the procedure at both follow-up moments (Table 8.2).

Appetite

Analyses of VAS scores are presented in Table 8.3. One patient was excluded because of missing data at one of the follow-up moments. The quantity patients wanted to eat in the fasted state was lower at one month compared to baseline (p=0.002), while feelings of fullness (p=0.016) and satiety (p=0.001) were increased. Median total AUC of desire to eat and prospective snacking showed a statistically significant decrease, while fullness was increased, one month and one year after the procedure. AUC of quantity and hunger decreased while satiety increased after the procedure, but the differences were only statistically significant at one-month follow-up. AUC of thirst did not change after the procedure. The graph of desire to eat is presented as an example of VAS evolution over postprandial time (Figure 8.1). There was no correlation between change in VAS scores and EWL.

Food reward

Liking scores for several food categories, corrected for stationary scores, changed statistically significantly over time, both before as well as after ad libitum lunch (Figure 8.2). One patient could not be included in the analysis because of missing data due to technical problems. Relative liking of bread and (sandwich) fillings were decreased before as well as after lunch, 12 months after the procedure. For both categories a meal induced decrease was observed only at the 12 months follow-up moment. Relative liking scores for drinks were statistically significantly lower only before lunch after one and twelve months. In the deserts category, relative liking decreased statistically significantly before as well as after lunch, both after one and twelve months and in the candy category before lunch only at one month, while at both follow-up moments after lunch.

	baseline		one month			twelve months		
	median	IQR	median	IQR	p	median	IQR	p
Ad libitum meal intake (kJ)	3704	2560 – 4626	2030	1466 – 2200	0.010*	2510	1752 – 3109	NS
Gastric emptying t½ (min)	136	122 – 150	134	94 – 164	NS	142	103 – 207	NS

Table 8.2 | *Ad libitum meal intake and gastric emptying half time. Data are expressed as median (IQR: 25th-75th percentile). * statistically significant difference compared to baseline (Friedman p<0.05 and Wilcoxon post-hoc p<0.025).*

VAS-score	baseline		one month			twelve months		
fasted (mm)	median	IQR	median	IQR	p	median	IQR	p
Desire to eat	59	17 – 72	54	22 – 62	NS	44	15 – 61	NS
Quantity	53	16 – 72	18	6 – 28	0.002*	30	18 – 43	NS
Fullness	17	4 – 31	45	33 – 52	0.016*	34	4 – 69	NS
Hunger	54	8 – 73	49	17 – 52	NS	38	18 – 61	NS
Snacking	9	2 – 33	9	2 – 12	NS	13	1 – 22	NS
Thirst	75	61 – 91	65	62 – 73	NS	63	43 – 81	NS
Satiety	9	2 – 25	41	31 – 52	0.001*	34	12 – 65	NS
AUC (cm*min)	median	IQR	median	IQR	p	median	IQR	p
Desire to eat	1046	686 – 1472	417	167 – 727	0.002*	629	383 – 1258	0.020*
Quantity	865	539 – 1434	317	177 – 641	0.004*	617	284 – 1204	NS
Fullness	723	344 – 1142	1596	1293 – 1892	0.002*	1261	977 – 1651	0.010*
Hunger	1066	773 – 1488	561	282 – 759	0.004*	757	533 – 1267	NS
Snacking	580	422 – 1190	160	23 – 599	0.016*	336	53 – 1095	0.016*
Thirst	1310	758 – 1751	1223	762 – 1644	NS	1147	497 – 1397	NS
Satiety	504	309 – 1400	1678	1153 – 2098	0.016*	1265	968 – 2001	NS

Table 8.3 | *Fasted scores and total area under the curve (AUC) of VAS for appetite at baseline, one month and twelve months after gastroplication. Data are expressed as median (IQR: 25th-75th percentile). VAS = Visual Analogue Scale; IQR = interquartile range. * statistically significant difference compared to baseline (Friedman p<0.05 and Wilcoxon post-hoc p<0.025).*

The corrected wanting scores were not statistically significantly different for all categories. (Figure 8.3). Four patients were excluded because of missing data due to technical problems with the computer software.

Eating behavior

Table 8.4 demonstrates the scores on the TFEQ and EDEQ at baseline and after 3 and 12 months. Uncontrolled eating and emotional eating scores in the TFEQ decreased statistically significantly after 3 months. An increase towards baseline values was observed in both subscales after one year; while uncontrolled eating remained statistically significantly lower compared to baseline, emotional eating did not. Cognitive restraint scores showed a trend towards increase. The restraint sub-scale in the EDEQ similarly showed an increase that did not reach statistical significance. Weight concern and shape concern scores decreased statistically significantly from baseline at 3 months and one- year follow-up. The global score on the EDEQ was only decreased after one year. There was no correlation between changes in TFEQ scores or EDEQ scores and EWL.

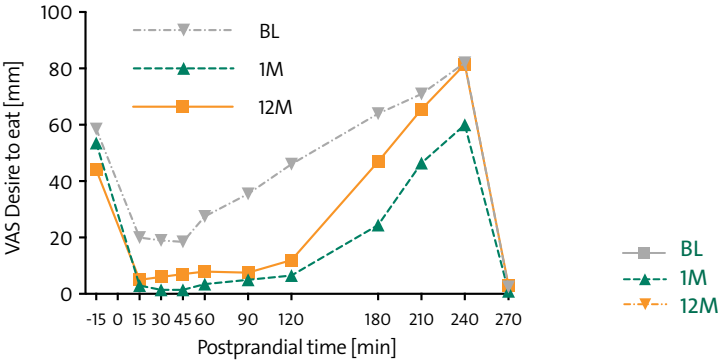

Figure 8.1 | *Median VAS scores for desire to eat. AUC statistically significantly different BL vs 1M p=0.002; BL vs 12M p=0.020 (Table 2). VAS=visual analogue scale.*

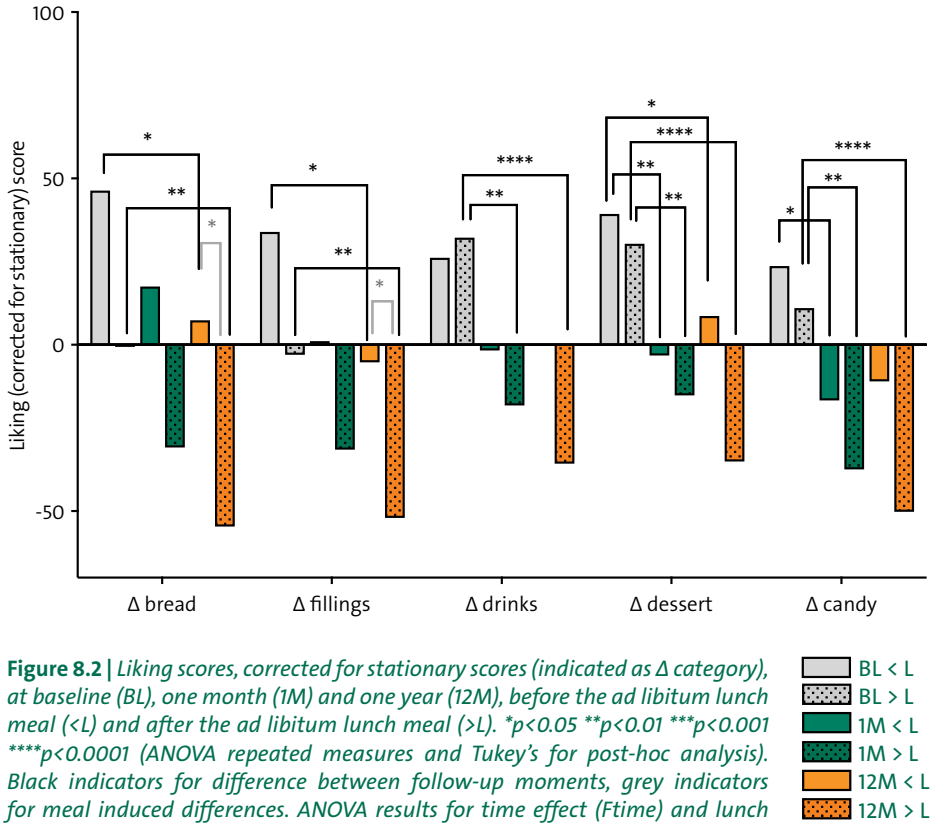

Figure 8.2 | *Liking scores, corrected for stationary scores (indicated as Δ category), at baseline (BL), one month (1M) and one year (12M), before the ad libitum lunch meal (<L) and after the ad libitum lunch meal (>L). *p<0.05 **p<0.01 ***p<0.001 ****p<0.0001 (ANOVA repeated measures and Tukey's for post-hoc analysis). Black indicators for difference between follow-up moments, grey indicators for meal induced differences. ANOVA results for time effect (Ftime) and lunch effect (Flunch): ΔBREAD Ftime(2,32)=9.390 p=0.0006 Flunch(1,16)=11.07 p=0.0043; ΔFILLINGS Ftime(2.320=10.60 p=0.0003 Flunch(1,16)=7.259 p=0.0160; ΔDRINKS Ftime(2,32)=14.62 p<0.0001 Flunch(1,16)=1,055 p=0.3196; ΔDESSERT Ftime(2,32)=18.76 p<0.0001 Flunch(1,16)=2.021 p=0.1743; ΔCANDY Ftime(2,32)=12.41 p=0.0001 Flunch(1,16)=2.265 p=0.1518.*

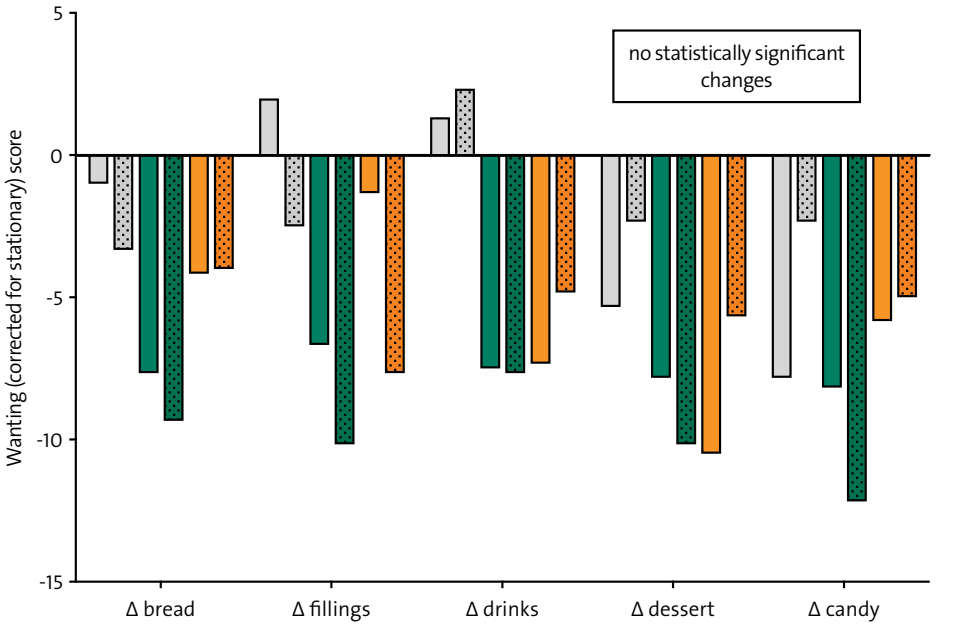

Figure 8.3 | *Wanting scores, corrected for stationary scores (indicated as Δ category), at baseline (BL), one month (1M) and one year (12M), before the ad libitum lunch meal (<L) and after the ad libitum lunch meal (>L). No statistically significant changes (ANOVA repeated measures).*

TFEQ	baseline		three months			twelve months		
	median	IQR	median	IQR	p	median	IQR	p
Cognitive restraint	45.2	32.5 – 62.3	61.5	48.8 – 81.7	N.S.	58.7	46.4 – 66.3	NS
Uncontrolled eating	51.8	40.7 – 74.1	14.8	3.7 – 26.9	0.007*	29.2	11.1 – 31.5	0.012*
Emotional eating	66.7	27.8 – 94.4	11.1	0.0 – 36.1	0.018*	22.2	0.0 – 72.2	NS
EDE-Q	median	IQR	median	IQR	p	median	IQR	p
Restraint eating	1.30	0.55 – 2.20	1.40	0.85 – 3.15	NS	2.20	0.90 – 3.40	NS
Eating concern	1.50	0.80 – 2.60	0.60	0.00 – 1.20	NS	0.60	0.20 – 1.50	NS
Weight concern	3.50	2.90 – 3.73	1.40	0.58 – 2.73	0.015*	1.20	0.55 – 2.25	0.007*
Shape concern	4.13	3.78 – 4.53	1.25	0.69 – 2.88	0.013*	1.38	0.38 – 2.69	0.008*
Global	3.15	2.47 – 3.37	1.30	0.54 – 2.61	0.037	1.39	0.83 – 2.59	0.012*

Table 8.4 | *Three Factor Eating Questionnaire (TFEQ) and Eating Disorder Examination Questionnaire (EDE-Q. Data are expressed as median (IQR: 25th-75th percentile). * statistically significant difference compared to baseline (Friedman p<0.05 and Wilcoxon post-hoc p<0.025).*

DISCUSSION

The main objective of this study was to evaluate eating behavior and food reward in a sample of patients that underwent a novel endoscopic gastroplication procedure for the treatment of obesity. We published before that the treatment is safe and results in continuous weight loss up to one year after the procedure. 38% excess weight loss after one year is relatively modest compared to RYGB and LSG (65–70% EWL), but adequate compared to other transoral stapling techniques (2, 3). Our findings in this study support the efficacy of the new method.

After endoscopic gastroplication with the ACE stapler, ad libitum food intake was decreased. Despite reduced food intake, desire to eat and anticipated snacking were smaller while feelings of fullness and satiety were higher. Even in the fasted state, the quantity patients wanted to eat was decreased and feelings of fullness and satiety increased compared to baseline. In contrast, hunger was not found to be different in the fasted state. We did not measure feelings of illness or distress, which might influence fullness and satiety more than hunger. This limitation should be addressed in future studies. The effects on ad libitum food intake and appetite scores that we found were most obvious at one month, but seem to persist up to one year, although to a lesser extent.

It was anticipated that gastric emptying rate could be influenced by plicating the stomach. Some authors found increased gastric emptying rate after sleeve gastrectomy and believe this is part of its success (25-27). Others found no changes after sleeve gastrectomy or adjustable gastric banding (28, 29). Procedures that alter gastric emptying rate may interfere with satiety because of changed timing of nutrient exposure to the small intestine (30, 31). However, we found that gastric emptying rate does not change after endoscopic gastroplication.

Wanting of food items did not change after the procedure, while liking was clearly decreased. This effect was obvious before as well as after ad libitum food intake for all categories except drinks. It appears that our patients' attention has shifted away from food after endoscopic gastroplication. Previous research has shown that food 'liking and wanting' are independent processes regulated by different neurobiological systems. A study by Finlayson et al. in healthy humans showed that wanting, but not liking, is changed by the ingestion of an ad libitum meal (32). Liking and wanting was also studied after RYGB. Both humans with morbid obesity as well as obese rats after gastric bypass surgery demonstrated reduced liking of high-versus low-calorie foods, but also markedly decreased wanting of particularly high-calorie food items (33). Wanting is more closely related to energy homeostasis than liking, which appears to be more stable in our patients compared to patients after gastric bypass.

Several authors used other methods to investigated food reward after traditional bariatric procedures. Ochner et al. used fMRI to assess neural responsivity pre- and post-operative to RYGB surgery and found significant changes in the fasted state; including in reward related and inhibitory areas of the brain (16). Miras et al. observed a 50% decreased reward value of chocolate candy in the fasted state after RYGB (15). Giel et al. used eye-tracking to investigate food cue processing after LSG and, like ourselves, found that attention shifted towards non-food cues after surgery. This can be interpreted as reduced food reward, associated with increased cognitive control (14). Furthermore, Bruce et al. used fMRI pre and post laparoscopic adjustable gastric banding (LAGB) to show decreased brain activation to food- versus non-food stimuli in regions implicated in food motivation and reward, while it showed increased brain activation in areas implicated in cognitive control and inhibition (13).

VAS scores confirmed that patients were satiated while performing the second computer task. However, we could not replicate the fasted versus satiated wanting changes that Finlayson et al. showed. This may be explained because of a small sample size (6 patients included), because our patients were may not have been completely fasted 4 h after breakfast or because food reward mechanisms are different in our group of patients.

We did find pre- versus post-lunch differences in liking of bread and (sandwich) fillings, but only 12 months after the procedure, which shows that attention has shifted even further away from food in the satiated gastroplicated patient.

An altered attitude towards food is also reflected in the eating behavior questionnaires. Patients experience less uncontrolled and emotional eating as measured with the TFEQ. To our knowledge, the TFEQ has not been utilized in other volume-reducing surgery studies, but Laurenius et al. showed similar results (decreased uncontrolled eating and emotional eating) after RYGB surgery at 6 weeks, one and two years follow-up (34). Abu Dayyeh et al. tried to explain the same changes after RYGB and found that uncontrolled eating was associated with gastro-jejunal stoma diameter (35). Stoma diameter is associated with the amount of restriction, which could explain the similarity with volume restriction by gastroplication.

We have to highlight that the TFEQ was not developed for evaluation of surgical interventions, therefore the results may not only reflect cognitive changes, but also physical restriction of stomach capacity, or stoma diameter, because of questions like 'Sometimes when I start eating, I just can't seem to stop', which are supposed to reflect uncontrolled eating. The EDE-Q was also used to assess eating disorder psychopathology. It is encouraging that our patients have a more positive self-image; they score statistically significantly lower on the EDE-Q items 'weight concern' and 'shape concern', which is also reflected in a decreased global EDE-Q score. Morseth et al. also

found a decreasing trend in global EDE-Q score after RYGB and BPD (biliopancreatic diversion) surgery, although at 5 years follow-up global EDE-Q score increased after RYGB (36).

This pilot study is obviously limited by the lack of a control group. We cannot yet be sure to which extent our findings are caused by gastroplication and what the effect of weight loss alone would have been. We believe the ACE stapling procedure contributes to changed hedonic hunger mechanisms leading to reduced food intake, combined with or induced by physical limitation of the stomach's capacity. The positive changes in behavior and self-image are most obvious at short-term follow-up moments, while the effect wears down at the one-year follow-up moment. This finding acknowledges that the strongest treatment effect is within the first year and not after. Weight regain is a topic of concern after all bariatric procedures (37). A part of the puzzle as to why patients regain weight after successful weight loss may be explained by our findings. We support the concept of adding bariatric surgery to combined lifestyle intervention, including behavioral interventions, instead of treatment with bariatric surgery alone. However, evaluation of eating behavior and food reward mechanisms should be included in future randomized trials to further elucidate the effects of either endoscopic gastroplication versus traditional bariatric surgery, or versus diet induced weight loss alone.

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Multicenter, Phase 1, Open Prospective Trial of Gastric Electrical Stimulation for the Treatment of Obesity: First-in-Human Results with a Novel Implantable System

ABSTRACT

BACKGROUND AND AIMS

To assess safety of the Exilis™ gastric electrical stimulation (GES) system and to investigate whether the settings can be adjusted for comfortable chronic use in subjects with morbid obesity. Gastric emptying and motility and meal intake were evaluated.

METHODS

In a multicenter, phase 1, open prospective cohort study, 20 morbidly obese subjects (17 female, mean BMI of 40.8 ± 0.7 kg/m²) were implanted with the Exilis™ system. Amplitude of the Exilis™ system was individually set during titration visits. Subjects underwent two blinded baseline test days (GES ON vs. OFF), after which long-term, monthly follow-up continued for up to 52 weeks.

RESULTS

The procedure was safe and electrical stimulation was well tolerated and comfortable in all subjects. No significant differences in gastric emptying halftime (203 ± 16 vs. 212 ± 14 min, $p > 0.05$), food intake (713 ± 68 vs. 799 ± 69 kcal, $p > 0.05$), insulin AUC (2448 ± 347 vs. 2186 ± 204, $p > 0.05$), and glucose AUC (41 ± 2 vs.41 ± 2, $p > 0.05$) were found between GES ON and OFF. At week 4, 13, and 26, a significant ($p < 0.01$) reduction in weight loss was observed but not at week 52. At this time point, the mean excess weight loss (EWL) was 14.2 ± 4.5%.

CONCLUSION

Gastric electrical stimulation with the Exilis™ system can be considered safe. No significant effect on food intake, gastric emptying, or gastric motility was observed. The reduction in weight loss with Exilis™ GES was significant but short lasting. Further electrophysiological research is needed to gain more insight in optimal stimulation parameters and lead localization.

INTRODUCTION

Bariatric surgery is the only long-term effective treatment for morbid obesity. However, only a small percentage of potentially eligible subjects will ever undergo a bariatric procedure (1). Bariatric surgical procedures such as laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG), and Roux-en-Y gastric bypass (RYGB) (2, 3) modify gastrointestinal anatomy and physiology, require lifelong medical surveillance, and are associated with a considerable amount of complications and long-term adverse effects such as GERD, chronic vomiting, dumping syndrome, and nutritional deficiencies. Taking the abovementioned considerations into account, there is room for other, less invasive therapies for morbid obesity. In this respect gastric electrical stimulation (GES) has been studied for over a decade as a minimally invasive, anatomy-preserving alternative for traditional bariatric procedures for the management of morbid obesity (4, 5). The technique aims to impair gastric motor function and to modulate afferent signaling from the stomach, leading to delayed gastric emptying with prolonged gastric distension and enhanced satiety, thus resulting in decreased food intake and weight loss (6).

Initial results with the Transcend Implantable Gastric Stimulator (IGS) were promising, but consecutive double-blind randomized controlled trials initiated between 2000 and 2005 failed to show a clear beneficial effect on body weight relative to sham-stimulated controls (7–9).

Up to now, in the reported clinical trials, only a narrow range of stimulation parameters and electrode configurations have been evaluated. Most clinical data on GES for obesity have been obtained using a single pulse frequency and duty cycle setting (40 Hz, 2 s On-3 s Off). Unfortunately, the efficacy and functional implications of these settings have not been systematically explored, neither in animals nor in humans. Nearly all subjects in these prior GES clinical trials were implanted with a single model of bipolar intramuscular lead, embedded in the stomach wall near the middle of the lesser curvature.

In a 5-year period of extensive animal studies in rodents, canine, and swine, each major component of GES was systematically reexamined. It was shown that a pulse width of > 2.0 ms (10), a 40 Hz pulse frequency, continuous stimulation (16 h On-8 h Off), and pre-pyloric pulse delivery led to an optimal delay in gastric emptying, gastric distension, and reduction in food intake (10). Moreover, chronic, daily delivery of the GES treatment resulted in weight loss. The encouraging results of these animal studies have been used to define the required capabilities of the current Exilis™ system.

The aim of this feasibility study was to gain first-in-human experience, to assess safety of the GES system, and to investigate whether the settings can be adjusted for comfortable chronic use. Furthermore, we aimed to discover whether acute gastrointestinal (GI) and feeding effects, as observed in animals, could be reproduced in humans. In addition, we aimed to enhance understanding of the mechanisms of action by which GES induces weight loss. We hypothesized that GES for obesity would be safe, decrease food intake, and induce weight loss, possibly through a delay in gastric emptying.

METHODS

Study design

We initiated a multicenter, phase 1, open prospective cohort study conducted in the Netherlands and the USA. The study was approved by the medical ethics committee of all participating hospitals and was conducted in full accordance with the Declaration of Helsinki (latest amendment by the World Medical Association in 2013). Participants gave written informed consent prior to participation. This study was registered in the US National Library of Medicine (http://www.clinicaltrials.gov, NCT01823705).

Subjects

Patients were enrolled via the outpatient clinics of the participating hospitals. Patients were considered eligible to enroll in this study if they were weight stable, between 21 and 64 years of age and had a body mass index (BMI) of 40–45 kg/m² or 35–39.9 kg/m² with at least one weight-related comorbidity (e.g., nonalcoholic steatohepatitis, hypertension, dyslipidemia, obstructive sleep apnea, arthrosis). In case a subject was diagnosed with diabetes mellitus, the diagnosis had to be made within the last 7 years, had to be currently treated with oral agents only, and had to have an HbA1c ≤ 8%. Exclusion criteria were prior major GI surgery (including bariatric surgery), pregnancy or the intention to become pregnant, functional and/or motility disorders, and medical, surgical, or psychiatric conditions that would limit study participation. Possible candidates underwent evaluation by a psychologist and a dietician before they were included in the trial. They were excluded from participation if behavioral issues (personality disorder, depression, and/or binge eating) were observed.

Procedure

The system was implanted under general anesthesia. The implanted components (Figure 9.1) consisted of a pulse generator (IPG, Model VNT0016 Version 3, Medtronic, Minneapolis, USA) with implantable charge coil (ICC, Version 1, Medtronic, Minneapolis, USA) and two 35 cm insulated unipolar leads (Model 4351 M, Medtronic, Minneapolis, USA). The leads were laparoscopically implanted into the muscle wall of the gastric antrum and were placed 3 to 5 cm proximal to the pylorus and parallel to the lesser curvature. A fixation disk was used to suture the leads to the serosal surface of the stomach. During placement of the leads, upper endoscopy was performed to prevent intraluminal placement of the electrodes. If indicated, the leads were reinserted. When correct placement of the leads was confirmed, the distal ends were pulled through the skin incision of the caudal trocar and connected to the IPG. The IPG was implanted in a subcutaneous pocket (1.5 to 4.5 cm deep) off midline between the patient's iliac crest and ribs and sutured in place. A similar pocket for the ICC was created above the ribs in the subcostal region of the 9th rib along the anterior axillary line. The ICC receives electromagnetic energy through magnetic coupling with the external charge coil to recharge the IPG (Figure 9.1). ICC and leads were connected to the IPG, checked for integrity, and switched off at the end of the procedure with the programming interface (Figure 9.1). The final position of the entire Exilis™ system was recorded with a postoperative abdominal X-ray. The implant surgery was followed by a 2-week recovery period prior to continuation of the study protocol.

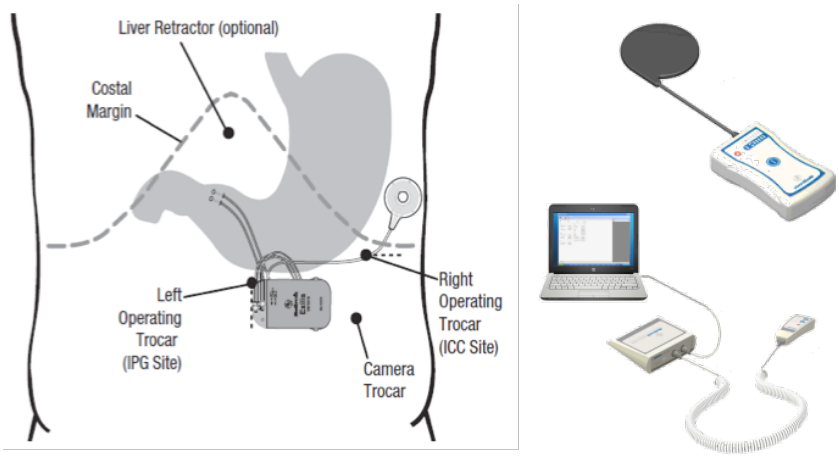

Figure 9.1 | *Implanted components (left), patient charging system (upper right) and external programming interface (lower right).*

Study protocol

The study protocol continued with four amplitude titration visits (visits A, B, C, and D) occurring at weekly intervals. During the first of these visits, the IPG was switched on, and subjects underwent sensory threshold tests in which they were exposed to stimulation at progressively higher amplitudes. Visit A was used to identify the lowest amplitude that caused any visceral sensation, while at the fourth and final titration visit, subjects were programmed to the highest comfortable pulse amplitude. Fixed parameters of the IPG were a pulse width of 5.0 ms, frequency of 40 Hz, and a continuous duty cycle for 16 h per day (off during 8 h at night). The amplitude titration visits were followed by two GI function test days performed in randomly assigned order and repeated twice (once with GES ON and once with GES OFF). Each GI function test day was preceded by a washout period (GES OFF) of 7 days, and subjects were blinded to the assigned GES treatment. Testing included simultaneous measurement of gastric emptying (using a stable isotope breath test), gastric motility (SmartPill®), plasma concentrations of glucose and insulin, and food intake over a 4-h period in the morning following an overnight fast (Figure 9.2). After completion of the GI function test days, each participant was programmed to GES ON (with the amplitude as determined during titration visit D), and long- term follow-up was started. Participants had to charge the IPG (by connecting the external charge coil to the ICC) once every 48 h. Monthly follow-up visits were planned during the first 12 months. Furthermore, GI function tests (with GES ON) were scheduled at weeks 26 and 52 of follow-up.

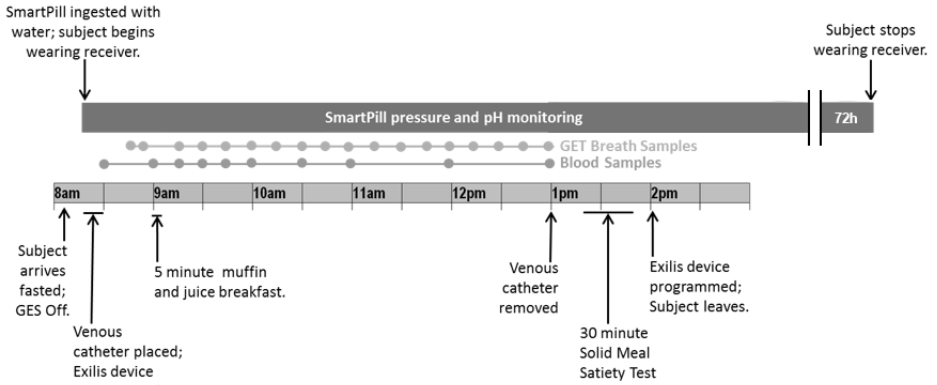

Figure 9.2 | *GI function testing*

GI function tests

Participants arrived at the hospital after an overnight fast. After programming of the GES device into ON or OFF mode (randomly assigned), baseline blood and breath samples were collected. In order to measure GI function, participants swallowed a SmartPill® (Buffalo, NY) and ingested a standardized breakfast muffin mixed with 13C-octanoic acid and 200 mL of orange juice (82 kcal, 19.2 g sugar). Blood and breath samples were collected at regular intervals during a 4-h period. Test days ended with the ingestion of an ad libitum pasta meal (in the Netherlands: Lasagna Bolognese; Plus Supermarket; energy density per 100 g: 160 kcal, 11 g carbohydrates, 7.1 g protein, and 9.4 g fat; in the USA: Macaroni and Cheese; Stouffer's; energy density per 100 g: 142 kcal, 15 g carbohydrates, 6 g protein, and 6 g fat), which participants could eat until comfortably full.

Gastric emptying

Gastric emptying was determined by using the gastric emptying breath test kit provided by Metabolic Solutions, Inc. (Nashua, NH). As mentioned above, 100 mg of 13C-octanoic acid was mixed into the standardized breakfast muffin (350 kcal, 64 g carbohydrates, 9 g protein, 7 g fat) ingested at t=0. Breath samples of $^{13}CO_2$ were obtained twice at baseline and every 15 min for 4 h following ingestion of the breakfast meal. Samples were analyzed using a gas isotope ratio mass spectrometer, and gastric emptying halftime and lag time were calculated using the Ghoos model (11).

SmartPill®

A wireless motility capsule (WMC, SmartPill®, Buffalo, USA) was used to obtain pressure data of the stomach and small intestine. The WMC has several sensors that monitor pH, pressure, and temperature and transmits these data to a receiver. Our participants swallowed the SmartPill® after consuming breakfast (breakfast muffin with orange juice) at each GI function test. Subjects wore the data receiver to enable continuous data collection from the capsule for 72 h (or until the capsule was passed during a bowel movement). The motility index was calculated as follows: Ln(sum of pressure amplitudes × number of contractions (Ct) + 1) (from Camilleri et al., 1985) (12).

Blood samples (glucose and insulin)

Sodium fluoride and SST II Plus gold tubes (Becton & Dickinson, New Jersey, USA) were used for determination of serum glucose and insulin, respectively. Glucose measure-

ments were performed on an Olympus AU 640/2700/5400 (Olympus, Tokyo, Japan). SST II Plus gold tubes were stored at room temperature for 30 min before centrifugation at 3000 rpm, 20 °C for 15 min. Serum insulin was measured using the Linco Human Insulin-specific RIA (HI-14 K) on a gamma counter with an inter-assay precision of 2.9–6.0%.

Quality of life questionnaires

The Impact of Weight on Quality of Life-Lite (IWQOL-Lite) and the Multi-purpose Short Form Survey-12 (SF-12) were used to measure quality of life. Both surveys were administered at screening visit, week 0, 13, 26, and 52 postoperatively. The SF-12 health survey consists of 12 questions extracted from the SF-36 survey. It includes both a physical (PCS) and mental component score (MCS). A higher score indicates generally better health (13). The IWQOL-Lite consists of 31 questions extracted from the longer IWQOL (74 questions). An increase of 7–12 points indicates a meaningful improvement in quality of life (14).

Statistical analysis

Statistical analyses were performed using SPSS 23.0 (IBM Corporation, Somers, NY). Data were visually checked for normality and for constant variance of residuals by plots of residuals vs. corresponding predicted values. If data were not normally distributed, log transformation was applied for further analysis of the data. Area under the curve (AUC) was calculated by the trapezoid rule. All variables were compared with a mixed analysis of variance model that included the fixed factor test day and random factor subject. For insulin and glucose (multiple time points per test day), time and the interaction between test day and time were added to the model. If a statistically significant intervention effect occurred, a post hoc Bonferroni test was performed. Data are presented as the mean ± SEM (unless specified otherwise) and considered significant at $p < 0.05$.

RESULTS

Participants

After screening 32 subjects, 12 were excluded for failure to meet inclusion criteria. A total of 20 subjects (3 male and 17 female with a mean age of 43.6 ± 1.6 years, a mean weight of 116.4 ± 4.1 kg, and a mean BMI of 40.8 ± 0.7 kg/m²) were included after giving informed consent and were implanted with the Exilis™ system. Considering comorbidities, one subject had diabetes mellitus, two had dyslipidemia, and five hypertension. The procedure was performed without any serious adverse events in all 20 subjects. All patients were discharged after one night, and none of the patients had to be readmitted. With the exception of incisional hernias which had to be corrected surgically (N = 2), all other adverse events were mild and could be treated conservatively or with medication therapy (Table 9.1). At 26-week follow-up, 3 subjects had withdrawn from the study due to not reaching the desired effect (N = 17 remaining). At 52 weeks follow-up, another 4 subjects had withdrawn for similar reasons (N = 13 remaining). Most of the patients who withdrew from the study had a surgical revision to RYGB or LSG. They were therefore not included in further analysis.

Adverse event	Action undertaken	N (%)
Misplacement of leads (inside stomach lumen)	replacement of leads	2 (10%)
Liver laceration	electrocautery	1 (5%)
Seroma at IPG site	none	3 (15%)
Wound infection at IPG site (superficial)	antibiotic therapy	3 (15%)
Incisional hernia	surgically corrected	2 (10%)

Table 9.1 | *Adverse events*

Amplitude titration visits

All 20 subjects were able to undergo the amplitude titration visits at the desired time. At the first titration visit (A), intended to determine the lowest amplitude that caused visceral sensations, 60% of the patients were set on an amplitude of ≤ 8.5 mA. Eighty percent of subjects reached the maximum amplitude of 10 mA after titration visit two (B). Long-term follow-up started with 90% of subjects set to an amplitude of 10 mA (Table 9.2, amplitude settings).

Amplitude	A	B	C	D
≤5	2 (10%)	1 (5%)		
6	1 (5%)		1 (5%)	1 (5%)
7	3 (15%)			
8	2 (10%)			
8.5	4 (20%)	2 (10%)		
9	1 (5%)	1 (5%)	1 (5%)	1 (5%)
9.5	1 (5%)			
10	6 (30%)	16 (80%)	18 (90%)	18 (90%)

Table 9.2 | *Amplitudes after titration visit A, B, C and D*

GI function tests

Ingestion of the breakfast muffin meal caused increases in plasma glucose and insulin concentrations that were not significantly different between the 4 test days (Figure 9.3). Also, the areas under the curve (AUC) for glucose or insulin levels were not different between the 4 test days (Table 9.3). Gastric emptying halftime was not significantly different between GES ON versus OFF (202.9 ± 15.7 min versus 212.2 ± 13.6 min, respectively). At week 26, gastric emptying halftime was 191.6 ± 14.8 min, and at week 52, 161.6 ± 6.6 min, p=0.07. Food intake was not significantly different between GES ON versus OFF nor was food intake at week 52 significantly different from baseline (Table 9.3). The GI motility index calculated from the SmartPill® recording was not significantly different between GES ON versus OFF.

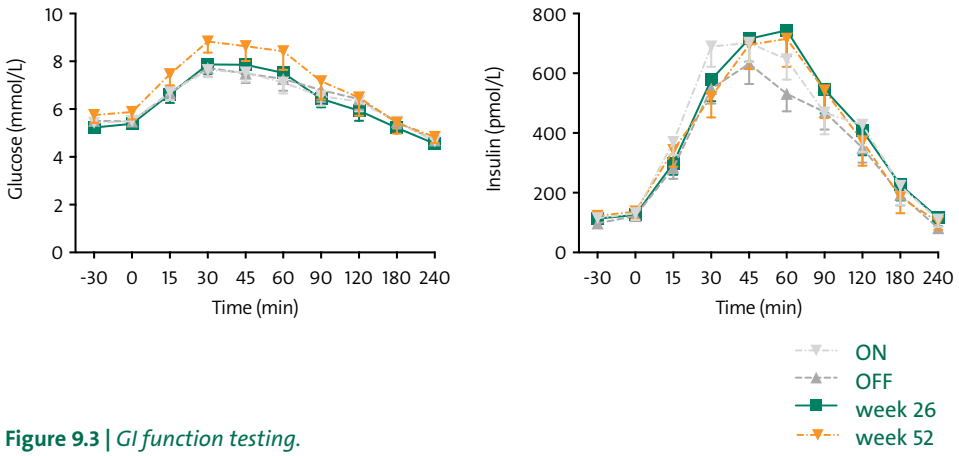

Figure 9.3 | *GI function testing.*

	Screening	ON	OFF	Wk 26	Wk 52	p
Insulin AUC (mmol/L.min)		2448 ± 347	2186 ± 204	2187 ± 301	2388 ± 278	0.47
Glucose AUC (mmol/L.min)		41.4 ± 1.5	41.4 ± 2.0	41.0 ± 1.5	43.3 ± 2.6	0.60
GE $t_{1/2}$ (min)	179.2 ± 8.3	202.9 ± 15.7	212.2 ± 13.6	191.6 ± 14.8	161.6 ± 6.6	0.07
Food intake (kcal)		712.7 ± 68.4	798.8 ± 68.9		800.2 ± 86.3	0.62
Motility index		53.4 ± 9.4	60.9 ± 10.5			0.60

Table 9.3 | *Results of GI function test (with follow-up). All data are presented as mean ± SEM. P values are for test day effects determined by mixed analysis of variance model. AUC: area under the curve, GE $t_{1/2}$: gastric emptying half time ON: GI function test with GES ON, OFF: GI function test with GES OFF, Wk 26: week 26, Wk 52: week 52.*

Weight follow-up

Mean body weight at baseline was 116.4 ± 4.1 kg and decreased significantly to 109.9 ± 4.3 kg at week 26 (p<0.01) as shown in Figure 9.4. At week 52, body weight was not significantly different from baseline. The mean percentage of excess weight loss (%EWL) at 4, 13, 25, and 52 weeks was 8.6 ± 2.1%, 11.1 ± 2.4%, 12.8 ± 3.7%, and 14.2 ± 4.5%, respectively (Figure 9.4).

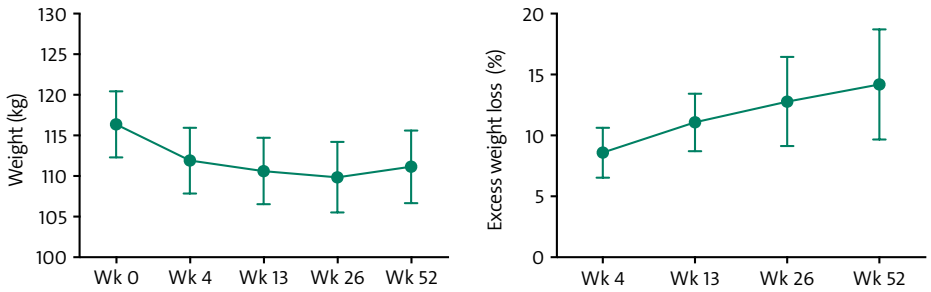

Figure 9.4 | *Weight (kg) and Excess weight loss (%) at Wk 0 (N=20), Wk 4 (N=20), Wk 13 (N=20), Wk 26 (N=17), Wk 52 (N=13). * p<0.005. ** p<0.01.*

Changes in systemic parameters and quality of life

No significant differences were observed in cholesterol levels, fasting glucose, HbA1c, and waist or hip circumference during the 1-year follow-up of this study (Table 9.4). Regarding QOL, significant differences were observed in SF-12 PCS and IWQOL-Lite total score. Mean SF-12 PCS improved from 41.3 ± 1.9 at screening to 46.6 ± 1.9 at 1-year follow-up ($p<0.05$). Mean IWQOL-Lite total score improved from 55.4 ± 3.8 at screening to 75.0 ± 3.4 at 1-year follow-up ($p<0.001$).

	Screening	Wk 0	Wk 13	Wk 26	Wk 52	p
Triglycerides	1.33 ± 0.13	1.26 ± 0.16	1.40 ± 0.20	1.22 ± 0.14	1.38 ± 0.16	0.75
HDL	1.20 ± 0.07	1.23 ± 0.09	1.24 ± 0.09	1.33 ± 0.10	1.34 ± 0.10	0.08
LDL	3.04 ± 0.19	3.13 ± 0.19	3.04 ± 0.16	3.03 ± 0.18	3.21 ± 0.20	0.85
Total cholesterol	4.84 ± 0.22	4.88 ± 0.24	4.88 ± 0.22	4.88 ± 0.21	5.10 ± 0.27	0.75
Fasting glucose	5.54 ± 0.19	5.45 ± 0.16	5.64 ± 0.18	5.42 ± 0.19	5.45 ± 0.20	0.33
HbA1c	5.60 ± 0.10	5.43 ± 0.07	5.48 ± 0.07	5.45 ± 0.07	5.50 ± 0.11	0.35
Waist circumference	122.4 ± 3.2	114.1 ± 5.1	115.9 ± 3.0	114.6 ± 3.4	118.7 ± 3.2	0.08
Hip circumference	131.3 ± 1.9	122.9 ± 4.8	125.5 ± 1.9	125.8 ± 2.2	127.8 ± 1.7	0.1
SF-12 PCS	41.3 ± 1.9	44.4 ± 2.0	46.6 ± 1.7*	45.5 ± 1.7	46.6 ± 1.9*	<0.001
SF-12 MCS	53.5 ± 2.8	56.4 ± 2.7	55.7 ± 2.4	58.4 ± 1.8	56.6 ± 2.7	0.40
IWQOL-Lite total score	55.4 ± 3.8	67.8 ± 3.7**	70.8 ± 3.4**	74.0 ± 3.7**	75.0 ± 3.4**	<0.001

Table 9.4 | *Cholesterol, glucose, HbA1c, waist and hip circumference and SF-12 and IWQOL-Lite outcome. All data are presented as mean ± SEM. P values are for test day effects determined by mixed analysis of variance model. Significant differences were determined by using post hoc comparisons with Bonferroni's correction. Wk 0: week 0, Wk 13: week 13, Wk 26: week 26, Wk 52: week 52. * Significantly different from Screening, p<0.05. ** Significantly different from Screening, p<0.001.*

DISCUSSION

In this first-in-human study with the Exilis™ GES system, we have shown that the system can be used safely and that GES was induced without causing discomfort in any participant. Despite the absence of discomfort, subjects were able to accurately predict whether the pulse generator was switched on or off. At baseline, food intake and satiety were not significantly different between GES ON versus OFF. A significant reduction in body weight occurred until week 26. We observed an excess weight loss of 14% at 52 weeks. This percentage is comparable with data from studies of subjects on diet and/or exercise alone, but this effect should be considered as disappointing when compared to minimal invasive procedures, such as gastric banding (50%) or endoscopic gastroplication (35%) (3, 15). Despite moderate weight loss, ad libitum food intake did not differ statistically significantly between follow-up moments. Furthermore, we did not observe changes in plasma glucose and insulin levels, while some other bariatric procedures are known to improve glucose metabolism, independent from weight loss (16).

Up to now various devices with different patterns of electrical stimulation have been evaluated for the treatment of morbid obesity. The first open and uncontrolled clinical trials investigating the Transcend® Implantable Gastric Stimulator (Medtronic Inc.) reported excess weight loss (EWL) varying in the range of 20–30% after 29 months of stimulation (17). In the present study, we found a mean EWL of 14% at 52 weeks (corresponding with a mean weight loss of 6.5 kg). Our results are comparable to those found in the SHAPE trial investigating the Transcend® device and the studies using the Tantalus gastric electrical stimulatory device (DIAMOND™)(9, 18, 19). Interestingly, an open, uncontrolled study using the closed-loop gastric electrical stimulation system Abiliti® showed a mean EWL of 29% at 12 months (15). Although considerable variability in weight loss has been observed in several clinical studies, one could argue whether the abovementioned variations are related to differences in stimulation parameters, to anatomical localization of leads, to differences in stimulation paradigm, or to other factors. Extensive animal work preceding the present study focused on acquiring the most effective lead position and stimulation parameters. Based on the canine data, the Exilis™ system uses continuous (16 h per day), current-controlled, monophasic pulses (width of 5.0 ms) with alternating polarities and a fixed frequency of 40 Hz. Although an infinite variation in programmed parameters can be obtained, such as pulse width, frequency, and amplitude, it is evident that the total amount of energy delivered is of utmost importance. Yoa et al. expressed the energy delivered by GES in mA^2 and found in humans that the stimulation energy required

for the first visceral sensation varied between 112.5 and 480 smA², while the highest tolerated stimulation energy varied between 480 and 3840 smA² (20). These authors also found that the subjects who were most sensitive to GES showed the greatest response to stimulation at 112.5 smA², leading to a significantly decreased water intake and gastric emptying rate. The stimulation energy delivered by the Exilis™ pulse generator at the maximum amplitude of 10 mA is 1200 smA². Although this energy level is well within the viscerally sensible and therapeutic range, no changes in food intake or gastric emptying rate were observed in the present study. An explanation for this lack of effect despite adequate stimulation is not readily available. It is possible that the lead position or specific stimulation parameters did not deliver the same amount of energy through the gastric tissue. Although the leads were placed 1 cm apart in both procedures, we placed them through the serosa of the stomach, while Yoa et al. used a transoral technique and placed them through the mucosa. Furthermore, our subjects may have been less sensitive to GES. The finding that a relatively large amount of energy was needed for visceral sensation supports this assumption.

Previous human in vivo experiments have shown a correlation between visceral sensitivity to GES and gastric responses, such as gastric motility and food intake. A higher response was noted in subjects more sensitive to GES (20). A total of 30% of our subjects were titrated up to the maximum of 10.0 mA already at the first visit, before any visceral sensation had occurred (a higher setting was technically not possible). The amplitude that caused the first sensation varied greatly in the remaining subjects (Table 9.3), but in those who were more sensitive to GES, a greater clinical effect was not observed. Eventually, 90% of our subjects received chronic GES therapy at the highest technically feasible amplitude of 10 mA. The gradual increase in amplitude setting showed that subjects had milder visceral sensations at the fourth titration visit when compared to the first visit. This observation points to adaptation to GES after prolonged application and is in line with our findings that GES effects were most pronounced in the short postoperative period after implantation.

In the current study, we applied continuous (16 h a day) electrical stimulation with a standardized pulse width. In such a setting, adaptation to the signal may have occurred, eventually even resulting in loss of efficacy. Adaptation of the gastric smooth muscle to chronic GES for the treatment of obesity has been shown previously in a dog model (21). Pulses with higher amplitude (i.e., higher stimulation energy) or pulse sequences that are unlikely to induce adaptation might be necessary in order to achieve adequate and long-term gastric responses. This supposition might explain why a GES system, with less frequent meal initiated stimulation results in a greater and more persistent effect on food intake and weight loss (22).

In the present study, we report several adverse events. Most adverse events were related to the IPG pocket (seroma, infection, hernia) and are most likely due to the relatively superficial placement of the IPG in the loose subcutaneous tissue. Ideally, the IPG would be sutured to the abdominal fascia, which could, however, cause connectivity problems in patients with a significant amount of subcutaneous fat. There were 10% incisional hernias that required correction. To reduce this percentage, more care should be taken to close the fascia around the leads or to tunnel the leads through the rectus abdominis muscle. Contrary to the popular bariatric procedures, a clear advantage of the current technique is its reversibility: all devices can be explanted without interference with GI anatomy and function.

Our study has several limitations. Due to the aims and deliverables of this study – to assess safety and preliminary effectiveness of the Exilis™ system – a control group was not included. In all studies and trials on interventions for weight loss, a control group is required to fully assess efficacy. Several studies have shown between 12 and 14% of excess weight loss in the control groups, which is comparable with what we observed with the present study (9, 23). Therefore, we conclude that the additional effect of GES with the Exilis™ system with its current settings is limited. Up to now, substantial work with GES for the treatment of obesity has been performed, and results vary considerably. More essential basic research has to be performed before we come to clinical applications. Pacing protocols should be optimized to achieve physiologically and clinically useful outcomes. Essential electrophysiological knowledge of the human stomach is still lacking, and more basic electrophysiological research work should be done before proceeding to new pacing protocols (24). Potentially, high resolution mapping of gastric slow-wave activity and the effects of gastric pacing on these waves may be a method to assess whether pacing protocols will be effective (25). When optimal stimulation parameters have been assessed, we recommend that they will be tested in a blinded randomized placebo-controlled trial.

In conclusion, gastric electrical stimulation with the Exilis™ system can be considered as safe in humans. No significant effect on food intake, gastric emptying, or gastric motility was observed. The reduction in weight loss with Exilis™ GES was significant but short lasting. More basic electrophysiological research is needed to develop optimal GES paradigms.

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10

Summary and General Discussion

BACKGROUND

Since the first study for this thesis was initiated in 2010, the prevalence of obesity has only risen. In America from 25.4% to 28.6% in adults and from 12.5% to 14.4% in children and adolescents. In the Netherlands, the prevalence of adult obesity has increased from 17.7% to 20.4% and from 5.9% to 7.0% in children and adolescents (1, 2). These numbers illustrate that, despite all efforts, we are still failing to control the obesity epidemic. Prevention of overweight and obesity has great attention from governments, schools and local authorities, but the above numbers prove that there is still an increasingly large group of patients that have reached obesity before these efforts have become effective (3, 4).

Bariatric surgery is the only proven long-term effective treatment of morbid obesity (5, 6). In response to the epidemic, the number of annual bariatric procedures has increased dramatically: in the US from 158.000 to 228.000 between 2011 and 2017 (7) and in the Netherlands from 3.500 to 11.468 between 2007 and 2018. However, an estimated 350.000 Dutch patients currently meet the criteria for bariatric surgery (8, 9). Innovative minimally invasive approaches like endoscopic bariatric therapy are gaining acceptance as more effective than diet and lifestyle measures, while less invasive than traditional bariatric surgery. The safety and effectiveness of these procedures are being studied extensively (10).

We explored the boundaries of morbid obesity treatment by studying the applicability of bariatric surgery in adolescents and by introducing novel bariatric techniques into human practice.

BARIATRIC SURGERY IN CHILDREN AND ADOLESCENTS

In their updated 2018 guideline, the American Society for Metabolic & Bariatric Surgery (ASMBS) recommends not to withhold bariatric surgery from morbidly obese adolescents (11). In our Chapter 2 review we performed a meta-analysis on available literature in January 2014. We found published data for 538 laparoscopic adjustable gastric banding (LAGB) procedures, 495 Roux-en-Y gastric bypasses (RYGB) and 272 laparoscopic sleeve gastrectomies (LSG). By collaborating with the authors we were able to combine their data. All three procedures lead to substantial weight-loss in the short to medium term and impressive reduction of comorbidities, with acceptable complication rates. This indicates that surgical intervention is applicable in appropriately selected adolescents. However, we have to emphasize that the available literature was of limited quality, most studies being observational and heterogeneous. Nevertheless, the ASMBS drew their conclusions almost exclusively from the results of our review and a long-term follow-up article after RYGB by Thomas Inge in 2017; studying under-21-year-olds (12). Chapter 3 of this thesis consists of our own retrospective analysis of 10 adolescents that underwent LAGB. We found that 6 of 10 patients achieved >50% excess weight loss, but most of the weight was lost after the first postoperative year. We also found that most complications and reoperations occur after the first three years, in line with what was found by other researchers (13). When adjustable gastric banding fails, it can be successfully converted to a malabsorptive procedure, although a higher risk for complications should be considered (14).

Now bariatric surgery in adolescents is becoming more widely available it will be increasingly difficult to perform decent clinical research. The 2018 ASMBS guideline recommendations possibly withdraw bariatric surgery on morbidly obese adolescents from the research setting we should still be operating in. Moreover, they recommend only LSG and RYGB as first choice, while LAGB carries the lowest operative risk and is effective in most patients (Chapter 2 and Chapter 3). Furthermore, there may be late complications after RYGB and LSG which we are not yet fully aware of. For example, Watanabe et al showed that 69% of pregnant women after malabsorptive surgery developed gestational anemia, and their neonatal birth weight was lower than in women without anemia or who had LAGB or LSG (15). A known late complication after LSG is the development of GERD. Genco et al recently published that upward migration of the Z-line (by 3.6 cm) and biliary-like reflux was found in more than 70% of patients at 58 months follow-up. Even more worrying is that they newly diagnosed Barrett's esophagus in 17% of their patients. These endoscopic findings did not correlate with patient reported GERD symptoms, concluding that regular endoscopic surveillance is

necessary after LSG (16). LAGB should be considered as a first step in adolescents, since we expect that most patients will not need RYGB or LSG as a second step. We believe well-designed, preferably randomized controlled, trials are still needed to unravel the effects of bariatric surgery at young age. Therefore, we initiated the BASIC (Bariatric Surgery in Children) trial to study LAGB in adolescents, of which the study protocol is presented in Chapter 4.

The BASIC trial is designed as a randomized controlled trial to assess the effects of LAGB in morbidly obese adolescents after failed combined lifestyle intervention (CLI). We aim to provide high-level evidence on weight loss, safety, reduction of comorbidity, psychosocial well-being and eating behavior. Sixty adolescents aged 14-16 years were randomized into either continued CLI with LAGB or continued CLI alone. The last patients were included late 2018 and we will publish the one-year follow-up results in 2021. We expect to find significant differences in weight-loss and reduction of comorbidity with an acceptable complication rate and positive effects on quality of life, personality and eating behavior, based on our findings in the first two chapters. Furthermore, evaluation of non-alcoholic fatty liver disease, cardiovascular changes, sleep architecture, metabolic and endocrine processes and inflammatory status will teach us – for the first time – how these processes progress throughout time when therapy-resistant morbid obesity in adolescents is treated with restrictive surgery or not.

ENDOSCOPIC GASTROPLICATION WITH THE ACE STAPLER

In a multicenter first-in-human trial we demonstrated that endoscopic gastroplication with the articulating circular endoscopic (ACE) stapler is technically feasible and safe. By plicating the stomach, it's volume is reduced (Figure 10.1). One hundred sixty plications were created in 17 patients without significant problems, while weight loss was encouraging. These results are presented in Chapter 5.

One of the major strengths of the technique is that full-thickness serosa to serosa plications are created. Other novel endoluminal techniques like endoluminal vertical gastroplasty (EVG) and transoral gastroplasty (TOGA, Figure 10.2-A) used mucosa to mucosa apposition and at follow-up endoscopy many of the staple lines or stitches were dehiscent (17, 18).

Transoral gastroplasty (TOGA) with use of the TOGA system (Satiety Inc., Palo Alto, CA) creates a vertical gastroplasty along the lesser curvature of the stomach performed through a transoral endoscopy (19). Using suction, tissue from both the ante-

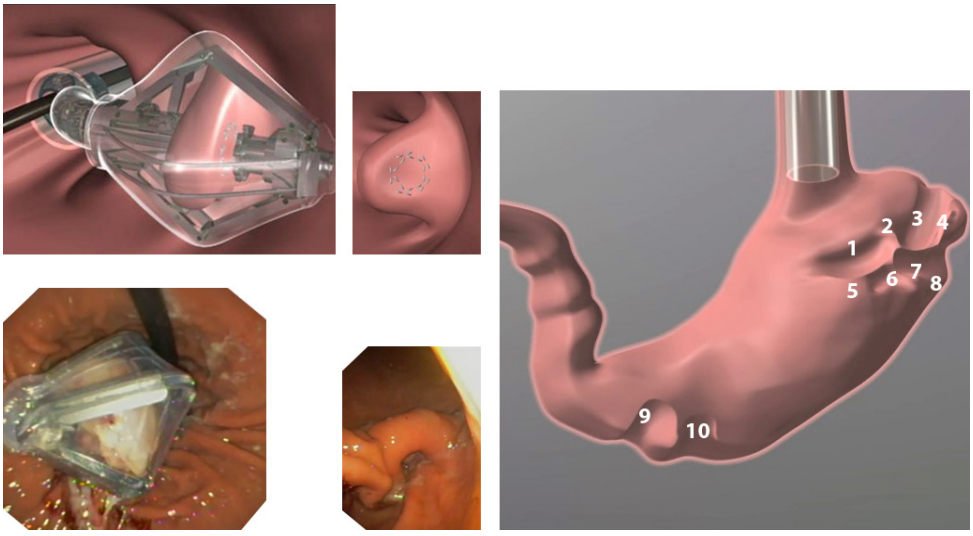

Figure 10.1 | *ACE stapling technique*

rior and posterior wall of the stomach are stapled together, connecting the anterior and posterior gastric walls from the angle of His to the lesser curvature. The first human study assessing the safety and efficacy of the TOGA system took place in 2008, in which 21 morbidly obese individuals with a mean BMI of 43.4kg/m² were enrolled. (20) After 6 months patients had an average EWL of 24.4%. No serious adverse events (SAE) were reported. However, at 6 months follow-up endoscopy, gaps in the staple line were observed in 13 out of 21 patients. After technical improvements of the device, a second human pilot study enrolled 11 patients (19). Average BMI decreased significantly from 41.6 kg/m² before treatment to 33.1 kg/m² at 6 months follow-up. The same results were seen in a multicenter trial with 1-year outcome, which involved 67 patients with a mean BMI of 41.5kg/m², which dropped to 33.1kg/m² at 6 months after the TOGA procedure (21). However, a multicenter randomized FDA trial was terminated secondary to lack of efficacy, whereafter the company dissolved, and future applications remain uncertain.

One year after endoscopic gastroplication with the ACE stapler, durability of stapled plications was confirmed by endoscopy. The primary obesity surgery endoluminal (POSE, Figure 10.2-B) procedure resembles the ACE stapling technique and also creates full-thickness serosa-to-serosa plications (22). Durability was not generally confirmed, but one example of intact plications during endoscopy at six months was presented (23). The POSE procedure is an approach in which a reduction of the gastric fundus is

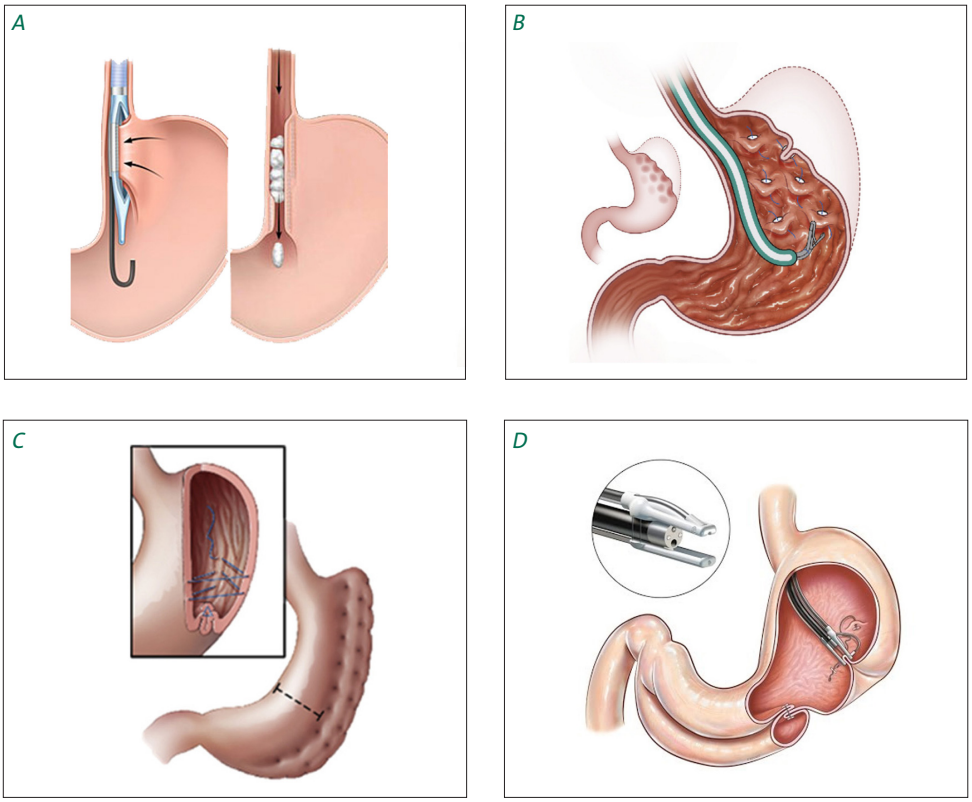

Figure 10.2 | *Endoscopic gastric volume reduction techniques. A TOGA; B POSE; C Overstitch; D Endomina.*

created, using a transoral incisionless operating platform (USGI Medical. San Clemente, CA, USA)(24). Transmural plications are placed at 8 to 9 locations in the gastric fundus with 3 additional plications in de distal part of the stomach, very similar to the ACE stapling technique. In order to create full thickness serosa-to serosa plications a special overtube-style platform is used (24). It has four working channels through which an endoscope and three additional instruments can be introduced: an endoscopic grasper, a flexible probe to assist in capturing target tissue and a suturing device. Current literature on the efficacy and safety of this device consist of two-open label prospective single-arm trials and two randomized controlled trials (24-27). In a multicenter randomized controlled trial in the US, 221 patients received the POSE procedure combined with low-intensity lifestyle interventions for a period of 12 months (27). They achieved a TBWL of 4.95 ± 7.04% , in comparison to 1.38 ± 5.58% in the control group, consisting of 111 patients who received low-intensity lifestyle intervention alone. Reported adverse events were vomiting (9%), nausea (1.6%) and pain (0.4%), which of-

ten required extended hospital stay. In addition, extra gastric bleeding (0.4%) and liver abscess (0.4%) occurred which required respectively open surgery and percutaneous drainage (27, 28). In another multicenter randomized controlled trial POSE-treated subjects showed 30% TBWL after 12 months compared to 5.9% in the control group (26).

Another system to create a restrictive sleeve is the Overstitch system (Apollo Endosurgery, Austin, Texas, USA; Figure 10.2-C). Contrary to the TOGA system, it applies full-thickness running sutures alongside the greater curvature of the stomach. This results in a reduction of the functional capacity of the stomach by up to 70%, a size comparable to the reduction of the gastric lumen in LSG (29). The Overstitch system consists of a double-channel endoscope equipped with a mounted suturing platform. A tissue grasper device is used to retracted the desired tissue into the suturing arm (30). After the Mayo Clinic first demonstrated the clinical safety and feasibility of this technique in 2013, multiple studies have also confirmed the efficacy of this procedure. A multicenter study among 3 centers, including 248 subjects with a baseline BMI of 37.8 kg/m², showed a total body weight loss (TBWL) of 18.6% at 24 months follow-up (31). Five (2%) serious adverse events occurred, including perigastric inflammatory fluid collection, hemorrhage due to splenic laceration, pulmonary embolism and pneumothorax. All patients recovered without need of surgical intervention. A recent retrospective analysis among 112 obese patients who underwent ESG using the Overstitch device reported comparable and consistent findings of approximately 15% TBWL at 6 months follow-up (32).

The Endomina sytem (EndoTool SA [SST], Gosselies, Belgium; Figure 10.2-D) reduces gastric volume by creating an full-thickness endoscopic gastroplasty alongside the greater curvature of the stomach (33). By using an over the scope triangulation platform attached to an endoscope, anterior-to-posterior greater curvature plications are applied. The stomach wall is mobilized and pulled back with a forceps. Under visual control a needle pierces the stomach wall at the designated site and a first anchor, attached to the suture is released. After the first plication is released, a second plication can be created with the same suture. The suture is than tightened and cut to appose the tissue of both plications. A single-center, phase 1, prospective cohort study was initiated in May 2015, which demonstrated 11% TWBL after 6-months. No major adverse event were observed in the 10 patients who underwent the procedure (33). In a multicenter prospective trial with 1-year follow-up in 30 patients, TBWL at 1 year was 7.4% (n=45). At follow-up gastroscopy, 88% of sutures were still in place. No SAE's were observed (34).

In order to gain more insight into the mechanisms of action of gastroplication with the ACE stapler we performed multiple additional studies. During several test days we collected blood samples, breath samples and questionnaires, patients performed

computer tasks and we collected gastrointestinal tissue samples from the gastric fundus, antrum and the duodenum. The results of these studies have shown interesting changes in perception of hunger and satiety, food intake, hormonal pathways, gene and enzyme expression, eating behavior and food reward.

In Chapter 6 we have shown that food intake, hunger and fullness and the release of the gut-derived peptides ghrelin, GLP-1 and PYY were altered. We found that plicating the stomach resulted in decreased hunger and increased fullness, paralleled by a fifty percent decrease of ad libitum food intake. Similar effects were demonstrated with the previously discussed POSE procedure, resulting in a significant improvement in satiation (35).

Ghrelin is a stomach-derived orexogenic hormone associated with nutritional status: it increases after a period of fasting and rapidly decreases after food intake (36). We found fasted ghrelin levels to be increased after gastroplication, confirming previous findings after LAGB, RYGB and gastroplication with the POSE system (37-40). Ghrelin decrease after food intake was stronger than before treatment with the POSE system (40). We observed a ghrelin response only after gastroplication and not before. It is likely that ingestion of our relatively small breakfast caused significant tension on mechanosensitive receptors of the plicated stomach, while the volume of the breakfast was too small to cause a similar response in the larger, unplicated stomach.

We also observed a weight loss induced decrease in the fasted levels of anoroxogenic hormones PYY and GLP-1 one month after the procedure, compared to baseline. This suggests a compensatory hormone response, to stimulate food intake and regain stable body weight. A decreased fasted PYY was also seen after gastroplication with the POSE system (40). Interestingly however is that one year after ACE stapling fasted PYY and GLP-1 were increased instead of decreased. This could mean that a new 'setpoint' has been established, providing a stronger satiating signal and possibly aiding in stable weight or even continued weight loss.

In Chapter 7 we studied plasma and tissue changes one year after the procedure. We observed a rise in plasma adiponectin and reduction of HbA1c, which is known to be caused by loss of excess body fat (48-51). Sharaiha et al studied the effects of ESG using the Overstitch device and found it accounted for a reduction in markers of diabetes (and hypertension and hypertriglyceridemia) in addition to sustained total body weight loss after a period of 24 months (52). Accordingly, we showed in Chapter 5 that reduction of oral diabetes medication and subcutaneous insulin use was achieved in our patients.

An interesting observation was that the mean gene expression of ghrelin and the enzyme GOAT (responsible for ghrelin acylation) in the tissue of the fundus, decreased after gastroplication. At the same time, plasma fasted active ghrelin was increased

and there was a positive correlation between the gene expression and its plasma values. Upregulated expression of ghrelin in the fundus was associated with greater increase in fasted ghrelin levels and downregulated expression with a smaller increase of ghrelin in the fundus 1 year after gastroplication. The implications of these changes in ghrelin are not fully understood and need further investigation.

Furthermore, for the first time, whole transcriptome changes in upper GI tissues were analyzed after a bariatric procedure. These analyses showed local downregulation of inflammatory tone in the fundus and duodenum. Reduced levels of inflammatory plasma markers are generally assumed to result largely from the reduction of visceral fat mass, which plays a major role in the low grade inflammatory state associated with obesity (53). Increasing evidence points to a link between intestinal inflammation status, obesity and diabetes (54-57). Based on the present study we cannot establish whether the apparent reduction of inflammatory tone in the upper gastrointestinal tract has a predominantly local cause, i.e. due to a changed food-intake pattern or digestion process, or whether it is a reflection of reduced low-grade systemic inflammation due to the reduction of body fat mass.

In the antrum, expression of gene sets related to cell cycle processes and extracellular matrix were increased. We speculate this relates to dilation of the stomach, a common observation after gastric volume reduction through other methods (58-61). While gastric volume was not quantified in our study, we perceived the stomach as larger during endoscopy at one-year follow-up than immediately after gastroplication.

The experiment presented in Chapter 8 evaluates the changes in food-reward mechanisms after gastroplication. Liking of food items was reduced after the procedure, while wanting did not change; an effect noted in de fasted as well as the satiated state. We also found meal induced (i.e. fasted vs satiated) changes in liking of bread and fillings, demonstrating that attention has shifted away from food in the satiated gastroplicated patient. Liking and wanting was also studied after RYGB. Both humans with morbid obesity as well as obese rats after gastric bypass surgery demonstrated reduced liking of high-versus low-calorie foods, but also markedly decreased wanting of particularly high-calorie food items (41). Wanting is more closely related to energy homeostasis than liking, which appears to be more stable in our patients compared to patients after gastric bypass. Other researchers also used functional MRI for brain imaging and also showed that reducing BMI was paralleled by a reduction in food-reward related signaling (42-45).

The three-factor eating questionnaire (TFEQ) was used to evaluate eating behavior. Patients experienced less uncontrolled eating after their stomach was plicated. The TFEQ has not been utilized in other restrictive procedures, but similar results were

found after RYGB surgery (46, 47). Patients also had a more positive self-image after therapy with the ACE stapling technique, as was reflected by the eating disorder examination questionnaire (EDE-Q).

In conclusion, we have shown that endoscopic gastroplication is safe and that it leads to reduced feelings of hunger and increased satiety; followed by reduced ad libitum food intake and significant weight loss in the first year. These changes are paralleled by advantageous changes in gastrointestinal hormone responses, despite unchanged gastric emptying rate. Patients experienced less uncontrolled eating and decreased liking of food after they were treated. Glucose metabolism improved, indicated by reduction of diabetes medication and reduced HbA1c. These studies have provided further insight into the mechanisms of action of endoscopic gastroplication. However, we found that most changes were stronger at one, than at twelve months follow-up. Chronic overeating may induce stretch on the stomach wall leading to dilation of the proximal stomach – a theory supported by increased cell cycle activity in the antrum - and possible reversal of the effect, similar to dilation of the gastric pouch in RYGB (62). Extending follow-up duration could elucidate on the extent of this reversal. Furthermore, we suggest to create additional plications in patients that are regaining weight or struggling with increased feelings of hunger if their one-year follow-up gastroscopy shows that there is space for more plications.

GASTRIC ELECTRICAL STIMULATION WITH THE EXILIS™ SYSTEM

Another novel approach to bariatric surgery is gastric electrical stimulation (GES). An electrical stimulator is implanted subcutaneously and its leads are laparoscopically connected to the stomach wall. This is an anatomy preserving technique that aims to change gastric motor function and/or feelings of satiety; thereby reducing food intake, which should lead to weight loss. Several GES systems have been developed and investigated in the past decades. Initial results with the Transcend implantable gastric stimulator (IGS) were promising, but consecutive double-blind randomized controlled trials initiated between 2000 and 2005, have failed to show a clear beneficial effect on body weight relative to sham-stimulated controls (63-65). In a five-year period of extensive animal studies the capabilities that are required for optimal GES were redefined, which led to the development of the current Exilis™ system (66).

In Chapter 9, we investigated the safety and feasibility of the system in a first in human experience. Although the procedure was technically feasible and safe, we

failed to provide any evidence supporting a beneficial effect. Neither gastric motor function, nor satiation or ad libitum food intake were significantly altered. After one year, weight was not significantly different form baseline. There was only a significant improvement in quality of life scores. We could not find an explanation why human test results were different from animal testing. The outcome of the extensive studies performed in the evaluation of the ACE stapler technique demonstrate once more how multifactorial obesity is and how many psychological and physiological systems are involved in weight loss. Furthermore, essential electrophysiological knowledge of the human stomach is still lacking. Probably, more basic electrophysiological research work should be done before proceeding to new pacing protocols (67). Potentially, high resolution mapping of gastric slow-wave activity and the effects of gastric pacing on these waves may be a method to assess whether pacing protocols will be effective (68). When optimal stimulation parameters have been assessed, we recommend that they will be tested in a blinded randomized placebo-controlled trial.

CONCLUSIONS AND FUTURE PERSPECTIVES

There is more research activity in morbid obesity than ever before. RYGB surgery and LSG have established a prominent place in the treatment of morbidly obese patients. However, there can be very valid reasons not to expose patients to a practically irreversible, anatomy altering procedure with potentially serious complications. Although we believe there is a place for bariatric surgery in the treatment of adolescent patients, selection should be done with utmost caution and in a transparent prospective research setting. It is too early to bring bariatric surgery to common practice as suggested by the ASMBS. Even when we assume bariatric surgery is safe and leads to weight loss, we do not know enough about the development of physical and mental comorbidity and its reversibility in the adolescent obese individual. Therefore, randomized studies like the BASIC trial are extremely important. The data we have collected comparing the operated – weight losing – morbidly obese adolescent with the weight-stable patient will give unique insight to obesity related morbidity and its reversibility.
Moreover, despite the increased number of bariatric procedures performed worldwide, only a small percentage of the morbidly obese population undergoes bariatric surgery. The reason as to why is multifactorial and includes (amongst others) costs, availability and fear of complications. New, minimally invasive or completely reversible procedures can possibly solve these problems and provide a solution for those who are now excluded. Procedures that are being applied in practice or investigated vary from

space-occupying devices like intragastric balloons to endoscopic stapling or suturing procedures, from malabsorptive devices such as the EndoBarrier system to botulinum toxin injection and from gastric electrical stimulation to vagal blocking (69). Even if it is difficult to reach the same amount of weight loss with these procedures as with traditional invasive procedures, we should continue to develop and study them, because if the results get close enough, with the current safety profile there is an enormous population to benefit from them. We believe we have shown that some minimal invasive techniques may have a future and that endoscopic gastroplication, but not gastric electrical stimulation in its current form, may lead to sustained weight loss, reduction of comorbidity and physiological as well as behavioral changes, with an excellent safety profile.

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Nederlandse Samenvatting

ACHTERGROND

Sinds de eerste studie voor dit proefschrift werd gestart in 2010, is de prevalentie van obesitas alleen maar gestegen. De Wereldgezondheidsorganisatie (Engels: World Health Organisation, WHO) rapporteerde een toename van 25.4% naar 28.6% bij volwassenen en van 12.5% naar 14.4% bij kinderen en adolescenten in Noord- en Zuid-Amerika. In Nederland is het aantal gevallen van obesitas bij volwassenen gestegen van 17.7% naar 20.4% en bij kinderen en adolescenten van 5.9% naar 7.0% (1, 2). Vanuit overheid, scholen en gemeenten wordt veel aandacht en geld besteed aan de preventie van overgewicht (3, 4). Echter, de toenemende prevalentiecijfers illustreren dat we er ondanks alle inspanningen niet in slagen de obesitas epidemie onder controle te krijgen.

Bariatrische chirurgie is de enige bewezen effectieve behandeling van morbide obesitas op de lange termijn (5, 6). Als reactie op de obesitas epidemie is het aantal bariatrische ingrepen per jaar drastisch toegenomen. Zo steeg het aantal ingrepen in de Verenigde Staten van 158.000 in 2011 naar 228.000 in 2017 (7). In Nederland werd het aantal bariatrische ingrepen verdrievoudigd over een periode van 11 jaar; van 3.500 geregistreerde ingrepen in 2007 naar 11.468 in 2018. Naar schatting voldoen echter 350.000 Nederlandse patiënten aan de criteria voor bariatrische chirurgie (8). Innovatieve minimaal invasieve behandelingen zijn steeds meer in opkomst. Uit onderzoek blijkt dat endoscopische bariatrische chirurgie effectiever kan zijn dan dieet- en leefstijlmaatregelen, terwijl het minder invasief is dan traditionele bariatrische chirurgie. De veiligheid en effectiviteit van deze behandelingen wordt momenteel uitvoerig onderzocht (9).

In dit proefschrift hebben we de grenzen van de behandeling van morbide obesitas verkend door de toepasbaarheid van bariatrische chirurgie bij adolescenten te bestuderen en vernieuwende bariatrische technieken als behandelmethode te introduceren.

BARIATRISCHE CHIRURGIE BIJ KINDEREN EN ADOLESCENTEN

In haar nieuwste richtlijn raadt de Amerikaanse vereniging voor bariatrische chirurgie (ASMBS) aan om bariatrische chirurgie in te zetten voor morbide obese adolescen-ten (10). Hoewel er veelbelovende onderzoeksresultaten zijn, mag dat advies als voorbarig worden beschouwd. In **Hoofdstuk 2** wordt een meta-analyse gepresenteerd over bariatrische chirurgie bij patiënten jonger dan 18 jaar. Uit de resultaten van 538 laparoscopisch geplaatste maagbanden, 495 gastric bypasses (maagomleidingen) en 272 laparoscopische maagverkleiningen blijkt dat alle drie de procedures tot substantieel gewichtsverlies op de korte en middellange termijn leiden. We concluderen dat chirurgische interventies voor de behandeling van obesitas toepasbaar zijn bij zorgvuldig geselecteerde adolescenten, mede gezien het relatief beperkte aantal complicaties. Bovendien was de afname van aan obesitas gerelateerde ziekten (zogenaamde comorbiditeit) indrukwekkend na alle drie de behandeltechnieken. Er moet echter benadrukt worden dat de beschikbare literatuur van matige kwaliteit is, waarbij de meeste studies observationeel en heterogeen zijn. Desondanks trok de ASMBS zijn conclusies vrijwel volledig op basis van onze analyse, gepaard met een lange-termijn studie van Thomas Inge in 2017 over gastric bypass chirurgie, waarin de bovengrens van adolescentie niet 18, maar 21 jaar was (11).

Hoofdstuk 3 van dit proefschrift bestaat uit een retrospectieve analyse van 10 adolescenten (jonger dan 18 jaar) die een maagband kregen. Uit onze resultaten bleek dat 6 van de 10 patiënten meer dan 50% van hun overgewicht kwijtraakten, maar dat het meeste gewicht werd verloren na het eerste postoperatieve jaar. De meeste complicaties traden op na drie jaar, overeenkomstig met wat andere wetenschappers constateerden (12). Bij de patiënten waarbij een maagband faalde, kon er succesvol worden geconverteerd naar een andere procedure. De aanbevelingen uit de richtlijn van de ASMBS uit 2018 zorgen er mogelijk voor dat bariatrische chirurgie bij adolescenten wordt aangeboden als reguliere zorg, waardoor het wordt teruggetrokken uit de onderzoeksomgeving waarin we ons gegeven de huidige stand van de wetenschap nog steeds zouden moeten begeven. Bovendien worden alleen de maagverkleining en de gastric bypass als eerste keuze aanbevolen, terwijl de maagband het laagste perioperatieve risico kent en effectief blijkt voor de meeste patiënten (**Hoofdstuk 2** en **Hoofdstuk 3**).

Wij zijn ervan overtuigd dat goed ontworpen studies, bij voorkeur gerandomiseerd en met een controlegroep, nog steeds nodig zijn om de gevolgen van bariatrische chirurgie op jonge leeftijd te ontrafelen. Om die reden zijn we de BASIC-trial (Bariatric Sur-

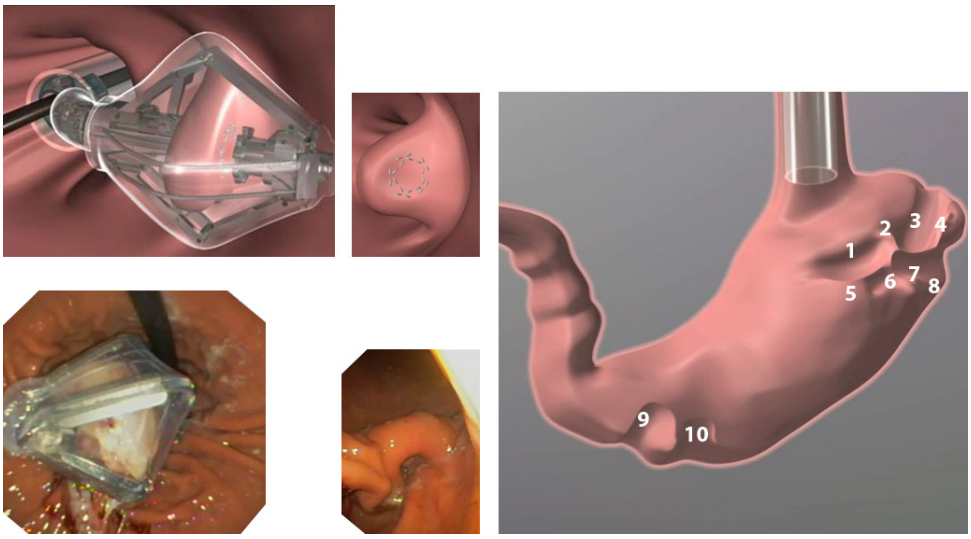
gery in Children) gestart, waarvan het protocol in **Hoofdstuk 4** wordt gepresenteerd. De BASIC-trial is een studie naar de effecten van een maagbandoperatie bij morbide obese adolescenten, waarbij gecombineerde leefstijlinterventie (GLI) heeft gefaald. We streven naar het leveren van hoogwaardig bewijs met betrekking tot gewichtsverlies, veiligheid, afname van comorbiditeit, psychosociaal welbevinden en eetgedrag. Bij zestig adolescenten in de leeftijd van 14 t/m 16 jaar werd door middel van randomisatie bepaald of een maagbandoperatie werd toegevoegd aan GLI. De laatste patiënten werden eind 2018 opgenomen in het onderzoek. Na 1 jaar follow-up, zullen de resultaten worden gepubliceerd in 2021. Op basis van eerder verricht onderzoek verwachten we significante verschillen in gewichtsverlies en afname van comorbiditeit, met een acceptabel percentage complicaties en positieve effecten op persoonlijkheid en eetgedrag. Bovendien zal deze studie inzicht geven in de ontwikkeling van niet-alcoholische leververvetting, cardiovasculaire veranderingen, slaappatroon, inflammatoire status, metabole en endocriene processen en zullen verschillen tussen beide behandelgroepen aan het licht komen.

ENDOSCOPISCH PLOOIEN VAN DE MAAG

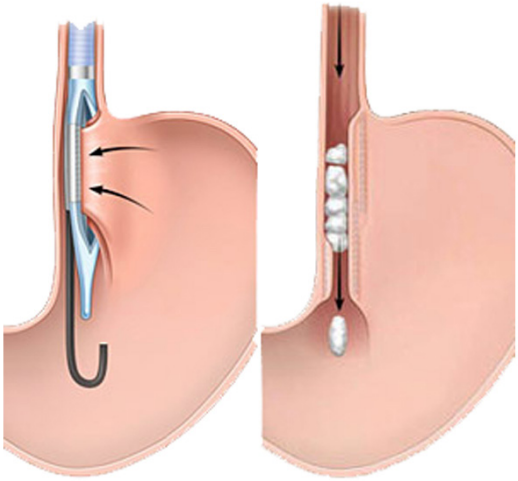
In Hoofdstuk 5 worden de resultaten van een multicenter studie gepresenteerd. In deze studie werd voor het eerst bij de mens gedemonstreerd dat endoscopische gastroplicatie met de Articulating Circular Endoscopic (ACE) stapler technisch haalbaar en veilig is. Door de maag te plooien wordt het volume verkleind (Afbeelding 1). Honderdzestig gastroplicaties werden gecreëerd bij 17 patiënten zonder significante problemen, terwijl het gewichtsverlies bemoedigend was.

Een van de grootste pluspunten van deze techniek is dat over de volledige dikte van de maagwand plooien worden gemaakt, waarbij serosa (buitenwand) tegen serosa komt te liggen. Het voordeel hiervan is dat de serosa kan vergroeien. Bij andere vernieuwende endoluminale technieken, zoals de verticale gastroplastiek (EVG) en transorale gastroplastiek (TOGA, Afbeelding 2), wordt mucosa (binnenwand) tegen mucosa gehecht. Bij endoscopische controle tijdens follow-up bleek dat veel van de nietjes of hechtingen los lieten (14, 15). In tegenstelling tot die bevindingen, blijven de plooien een jaar na endoscopische gastroplicatie met de ACE stapler wel behouden.

Om meer inzicht te krijgen in de manier waarop gastroplicatie van de maag tot gewichtsverlies leidt, hebben we meerdere aanvullende studies uitgevoerd. Gedurende een aantal testdagen verzamelden we bloedmonsters en vragenlijsten, patiënten voerden computertaken uit en we namen weefsel af uit de fundus van de maag, het antrum



Afbeelding 1 | *ACE stapling techniek*



Afbeelding 2 | *TOGA procedure*

en het duodenum. De resultaten van deze studies toonden interessante veranderingen in gevoelens van honger en verzadiging, vrijwillige calorie inname, hormonale reacties, gen- en enzymexpressie, eetgedrag en de belonende waarde van voedsel.

In **Hoofdstuk 6** laten we zien dat honger en verzadiging, vrijwillige calorie inname en de afgifte van de gastro-intestinale hormonen ghreline, glucagon-like-peptide-1 (GLP-1) en peptide YY (PYY) veranderen. We ontdekten dat het plooien van de maag resulteerde in afname van het hongergevoel en toename van verzadiging, gepaard gaande met een 50% afname van ad libitum (vrijwillige) voedselinname.

Ghreline is een honger bevorderend hormoon, met name afkomstig uit de maag, dat geassocieerd is met voedingsstatus: het neemt gestaag toe na een periode van vasten en daalt snel na de inname van voedsel (17). We constateerden dan ook dat het nuchter ghreline verhoogd was na gastroplicatie. Een daling van het plasma ghreline zagen we alleen na gastroplicatie en daarvoor helemaal niet. Het is aannemelijk dat inname van een relatief klein ontbijt significante rek veroorzaakt op de mechanosensitieve receptoren van de geplooide maag, terwijl het volume van datzelfde ontbijt te klein was om een soortgelijke reactie uit te lokken in de grotere, ongeplooide maag.

Bovendien zagen we een maand na de procedure een afname in de nuchtere spiegels van de honger remmende hormonen PYY en GLP-1. Deze compensatoire hormonale reactie om voedselinname te bevorderen en terug te komen op een stabiel lichaamsgewicht wordt waarschijnlijk veroorzaakt door het gewichtsverlies. Dit effect werd ook door andere onderzoekers na een vergelijkbare behandeling geconstateerd (21). Een interessante bevinding is echter dat nuchtere PYY en GLP-1 spiegels na een jaar juist verhoogd waren in plaats van verlaagd, wat zou kunnen duiden op het bereiken van een nieuw 'set-point', leidend tot een sterker verzadigingssignaal en daarmee een bijdrage leverend voor een stabiel of zelfs verder afnemend gewicht.

Het experiment dat in **Hoofdstuk 7** wordt gepresenteerd, evalueert hoe patiënten de belonende waarde van eten voor en na de ingreep ervaren. 'Liking' van etensmiddelen was verminderd na de procedure, terwijl 'wanting' onveranderd bleef; een effect dat opgemerkt werd in zowel de nuchtere als de verzadigde staat. We constateerden ook dat het effect van een maaltijd op 'liking' van brood en broodbeleg veranderd was, waaruit we kunnen afleiden dat er verminderde aandacht is voor eten bij verzadigde patiënten na gastroplicatie. Dit verschil werd pas na 12 maanden waargenomen. De Three-Factor Eating Questionnaire (TFEQ) werd gebruikt om eetgedrag te evalueren. Patiënten ervoeren minder ongecontroleerd eetgedrag nadat hun maag geplooid was. Daarnaast hadden patiënten een positiever zelfbeeld na behandeling met de ACE stapling techniek, zoals duidelijk werd middels de Eating Disorder Examination Questionnaire (EDE-Q).

In **Hoofdstuk 8** hebben we een jaar na de gastroplicatie plasma en weefselveranderingen bestudeerd. We observeerden een stijging in het plasma adiponectine en afname van HbA1c, waarvan bekend is dat dit veroorzaakt wordt door verlies van overmatig lichaamsvet (28-31). Deze bevindingen zijn in lijn met de verminderde behoefte aan diabetes medicatie, wat we reeds in **Hoofdstuk 5** hebben aangetoond.

Een interessante observatie was dat de gemiddelde genexpressie van ghreline en het enzym GOAT (verantwoordelijk voor de acetylering van ghreline) in het weefsel van de fundus afnam na gastroplicatie. Tegelijkertijd was het plasma ghreline juist verhoogd (**Hoofdstuk 6**), waarbij een positieve correlatie blijkt te bestaan tussen de genexpressie in het weefsel en de plasmawaarden. Dit houdt in dat toegenomen expressie van ghreline in de fundus geassocieerd was met een toename van nuchter ghreline terwijl verminderde expressie van ghreline zorgde voor een kleinere toename van nuchter ghreline in het plasma. De implicaties van deze veranderingen worden nog niet volledig begrepen en moeten verder worden onderzocht.

Daarnaast hebben we voor het eerst veranderingen in het volledige transcriptoom van proximaal maag- en darmweefsel geanalyseerd na een bariatrische ingreep. Deze analyses toonden downregulatie van inflammatoire activiteit in weefsel van de fundus van de maag en het duodenum. Verminderde spiegels van inflammatoire markers in plasma worden over het algemeen gezien als een gevolg van de afname van viscerale vetmassa, wat een belangrijke rol speelt in de laaggradige inflammatoire status die geassocieerd wordt met obesitas (32). Er bestaat dan ook toenemend bewijs dat er een link is tussen intestinale inflammatiestatus, obesitas en diabetes (33-36). Op basis van de huidige onderzoeksresultaten kunnen we niet vaststellen of de gebleken afname van inflammatoire tonus in het proximale maagdarmkanaal een voornamelijk lokale oorzaak heeft, door een veranderd voedselinname patroon of verteringsproces, of dat het een afspiegeling is van verminderde laaggradige systemische inflammatie op basis van de afname van lichaamsvetmassa.

In het antrum van de maag was de expressie verhoogd van genen die gerelateerd zijn aan de celcyclus en de opbouw van extracellulaire matrix. Dit zou verklaard kunnen worden door de geleidelijke dilatatie van de maag, een gebruikelijke bevinding na volumereductie van de maag (37-40). Hoewel het maagvolume niet gekwantificeerd werd in onze studie, imponeerde de maag tijdens de endoscopie een jaar na gastroplicatie groter dan meteen na de ingreep.

Concluderend hebben we in **Hoofdstuk 5 t/m 8** aangetoond dat endoscopische gastroplicatie veilig is en dat het leidt tot verminderde gevoelens van honger en toename van verzadiging, gevolgd door verminderde vrijwillige voedselinname en significant gewichtsverlies in het eerste jaar. Deze veranderingen gaan gepaard met voordelige

veranderingen in gastro-intestinale hormoonreacties, ondanks een onveranderde maagontledigingssnelheid. Patiënten ervoeren minder ongecontroleerd eetgedrag en verminderde 'liking' van eten nadat ze behandeld waren. Het glucosemetabolisme verbeterde, wat werd aangetoond door afname van het HbA1c en verminderde noodzaak tot het nemen van diabetes medicatie . Deze studies hebben inzicht gegeven in het werkingsmechanisme van endoscopische gastroplicatie. We toonden hierbij aan dat de meeste effecten sterker waren na 1 maand dan na 12 maanden follow-up. Chronisch overeten zou rek op de maagwand kunnen veroorzaken waardoor de proximale maag weer uitrekt – een theorie die ondersteund wordt door verhoogde celcyclus activiteit in het antrum van de maag – en het effect afneemt. Dit verschijnsel is vergelijkbaar met dilatatie van de pouch na gastric bypass chirurgie (41). Het uitbreiden van de follow-up duur in toekomstige studies zou opheldering kunnen geven over de mate waarin het effect afneemt. Daarnaast stellen we voor additionele plicaties te creëren bij patiënten die aankomen in gewicht of kampen met toename van hongergevoel een jaar na gastroplicatie.

ELEKTRISCHE STIMULATIE VAN DE MAAG MET HET EXILIS™ SYSTEEM

Een andere vernieuwende bariatrisch chirurgische techniek is de maagstimulator (gastro-elekrische stimulatie, GES). Een elektrische stimulator wordt onderhuids geïmplanteerd en laparoscopisch verbonden met de maagwand middels twee draden. Dit is een anatomiebehoudende techniek, waarbij beoogd wordt zowel de motorische functie van de maag als verzadigingsgevoelens te beïnvloeden. Hierdoor wordt voedselinname geremd, wat leidt tot gewichtsverlies. Verscheidene GES-systemen zijn ontwikkeld en onderzocht in de laatste decennia. De initiële resultaten met de Transcend stimulator waren veelbelovend, maar er werd geen duidelijk positief effect op gewicht geconstateerd in vergelijking met een groep die nep-stimulatie kreeg in verschillende dubbelblind gerandomiseerde studies (42-44). In een periode van vijf jaar werd uitgebreid dieronderzoek verricht, waarbij de specificaties die nodig zijn voor optimale GES opnieuw werden gedefinieerd (45). Dit heeft geleid tot de ontwikkeling van het huidige Exilis™ systeem.

In **Hoofdstuk 9**, onderzochten we de veiligheid en haalbaarheid van dit systeem voor het eerst in de mens. Daarnaast werd gekeken naar het effect van deze methode bij 20 patiënten. Hoewel de procedure technisch uitvoerbaar en veilig bleek, zijn we er niet in geslaagd bewijs te leveren voor een voordelig effect. Noch de motorische

functie van de maag, noch verzadiging of ad libitum voedselinname waren significant veranderd. Na een jaar was het gewicht niet significant verminderd ten opzichte van de baseline. Er werd enkel een significante verbetering in kwaliteit van leven gerapporteerd. We hebben geen verklaring kunnen vinden voor de discrepantie in resultaten tussen dieren en mensen. Het ontstaan van obesitas is multifactorieel en veel psychologische en fysiologische systemen zijn betrokken bij gewichtsverlies, zoals ook werd aangetoond met de uitgebreide studies die we in het het kader van de ACE stapler hebben gedaan. Bovendien ontbreekt essentiële elektrofysiologische kennis van de menselijke maag. Ons inziens zal er meer kennis over basale elektrofysiologische processen opgedaan moeten worden, voordat er verder wordt gekeken naar de mogelijkheden van nieuwe maagstimulatieprotocollen. Vervolgens kan door middel van high-resolution mapping van activiteit in de maag worden onderzocht of bepaalde instellingen effectief zullen zijn (47). Wanneer optimale stimulatie parameters vastgesteld zijn, raden we aan deze te onderzoeken in een geblindeerd placebogecontroleerde studie.

CONCLUSIES EN TOEKOMSTPERSPECTIEF

Er is momenteel meer wetenschappelijk onderzoek gaande naar het ontstaan en de behandeling van morbide obesitas dan ooit tevoren. De gastric bypass en de maagverkleining hebben een prominente plaats in de behandeling van morbide obese patiënten. Echter, er kunnen zeer valide redenen zijn om patiënten niet bloot te stellen aan deze onomkeerbare, anatomie veranderende procedure met potentieel ernstige complicaties. Hoewel we geloven dat er een plaats is voor bariatrische chirurgie in de behandeling van adolescente patiënten, moet selectie met grote zorgvuldigheid plaatvinden in een transparante onderzoeksomgeving. Het is te vroeg om bariatrische chirurgie naar de standaardpraktijk te brengen, zoals gesuggereerd wordt door de ASMBS. Zelfs wanneer we aannemen dat bariatrische chirurgie veilig is en leidt tot gewichtsverlies, weten we nog te weinig over de ontwikkeling van fysieke en mentale comorbiditeit bij adolescenten. Om die reden zijn gerandomiseerde studies zoals de BASIC-trial van groot belang.

Ondanks het toenemende aantal uitgevoerde bariatrische procedures wereldwijd, ondergaat slechts een klein percentage van de morbide obese populatie bariatrische chirurgie. De reden daarvoor is meerledig en bestaat onder andere uit kosten, beschikbaarheid en angst voor complicaties. Nieuwe, minimaal invasieve en/of compleet omkeerbare procedures kunnen deze problemen wellicht oplossen en uitkomst bieden

voor diegenen die nu buiten de boot vallen. Procedures die worden toegepast in de praktijk of worden onderzocht variëren van ruimte-innemende hulpmiddelen zoals de maagballon tot endoscopische staple- of hechttechnieken, van malabsorptieve technieken, zoals de EndoBarrier tot botuline toxine injecties en van maagstimulatoren tot vagusblokkade (48). Zelfs als er minder gewichtsverlies behaald wordt dan met traditionele invasieve procedures, moeten we deze technieken blijven ontwikkelen en bestuderen. Als de resultaten namelijk dicht genoeg in de buurt komen is er een enorme populatie die hiervan kan profiteren vanwege het lage complicatierisico. Al met al, lijkt er een toekomst weggelegd voor de behandeling van morbide obesitas door middel van enkele minimaal invasieve technieken. We hebben aangetoond dat endoscopische gastroplicatie, maar niet gastro-elektrische stimulatie in zijn huidige vorm, kan leiden tot blijvend gewichtsverlies, afname van comorbiditeit, fysiologische veranderingen en gedragsveranderingen.

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V

Valorisation

In the scope of a medical thesis, valorisation means "the process of value-creation out of knowledge, by making knowledge suitable and available for social or economic utilization and to translate this into high-potential products, services, processes and industrial activities" (Landelijke Commissie Valorisatie. Waardevol: Indicatoren voor Valorisatie; 2011). This thesis focuses on the boundaries of bariatric surgery as a treatment for (morbid) obesity. It has two main topics: the treatment of morbidly obese adolescents and the innovation of bariatric surgical practice, by developing novel medical devices.

Since 1975, the prevalence of obesity in the world has almost tripled. More than 650 million people are currently obese, of which approximately 40 million are adolescents (1). In the US 13% of adolescents qualify as extremely obese (2). In the Netherlands nearly half of all adults are overweight, while 14.2% qualify as obese. Among Dutch children and adolescents, the prevalence of obesity was 2.8% in 2017 (3). Obesity is associated with serious comorbidity (such as type 2 diabetes mellitus, cardiovascular diseases, sleep apnea, asthma and musculoskeletal disorders) (4-6). Currently most of the world's population lives in a country where obesity kills more people than malnutrition. The risk of dying from any obesity related cause increases by 6-7% for every 2 years lived with obesity (7). Furthermore, obesity reduces quality of life. For example, persistent obesity in women is associated with higher risk of never being gainfully employed and not having a partner (8). Obese adolescents are also likely to suffer from psychological morbidity which has the potential of scarring them for life (9).

The obesity epidemic therefore imposes a tremendous social and economic burden. Estimates of direct health care costs in the US range from $147 billion to $210 billion per year (10). In the Netherlands, 2.2% (€1.6 billion) of total health care costs was spent on obesity related diseases in 2012 (11). In addition, obesity is associated with indirect costs to society due to unemployment, absenteeism, lower productivity, premature mortality and disability. The costs of job absenteeism in the US are approximately $4.3 billion annually, while lower productivity at work costs employers $506 per obese worker per year (12, 13).

In the first part of this thesis we investigated the applicability of bariatric surgery in morbidly obese adolescents and initiated the BASIC trial, a randomized controlled trial in which the effects of gastric banding on weight loss, health and psychosocial wellbeing is studied extensively. The impact of adolescent obesity in the community and potentially successful treatment strategies was illustrated by frequent media attention; resulting in newspaper articles, interviews and television documentaries (14-19). If morbidly obese adolescents can be successfully and safely treated, their future role in society and their contribution to the community can change tremendously. Furthermore, once our findings are published, they are likely to change national and

international guidelines for the treatment of obese adolescents.

The second part of this thesis focuses on novel techniques with two specifically designed medical devices. One of these devices is the ACE stapler, designed by a small medical device company called BaroSense Inc. They raised money from investors to design, develop and test the device from drawing table, through animal testing, to the first test in humans. We provided the infrastructure to test the safety and preliminary efficacy of the technique and collaborated to further investigate its mechanisms of action, with their financial support. A novel technique becomes much more valuable to future investors and more credible to the international scientific community when mechanisms of action are unraveled. Although BaroSense Inc. was dissolved after they were unable to raise sufficient funds, the potential of the technique was recognized by Boston Scientific, that acquired their assets and invested to complete the study protocol.

The second device that we studied was the Exilis™ gastric electrical stimulator in collaboration with Medtronic. Again, this was primarily a study to assess safety and preliminary efficacy and financial support was provided to investigate mechanisms of action. The potential benefits for society are of interest to the press. Documentaries and interviews were made about the ACE stapler as well as the Exilis™ device (20-22). The ACE stapler has shown its potential and Boston Scientific profits from its success when the technique becomes commercially available. However, the initial results with the Exilis™ system were disappointing and Medtronic decided to stop the project for the time being. Our collaboration led to increased insight, but will not lead to any financial gain for Medtronic in the near future.

Traditional bariatric surgery has proven to be cost-effective. The exact numbers have not been analyzed in the Netherlands, but have been in our neighboring countries Germany and Belgium. Over 10 years, bariatric surgery generated 1.2 to 1.4 quality-adjusted life years (QALYs) with an incremental cost-effectiveness ratio of €2457 to €2809 per QALY. To put this in perspective, in the Netherlands up to €80.000 per QALY is regarded as cost-effective, depending on the severity of the disease (23). Over an entire lifetime, surgery led to savings of €8522 to €9332 and generated an increment of 3.2 to 5.0 QALYs. Furthermore, it was found that delaying surgery for up to 3 years, resulted in a reduction of 0.4 QALYs gained (24, 25). In this analytical model, the mean age was 40 years. Assuming that there are no 'very-long term complications' that we are currently still unaware of, it is likely that bariatric surgery at the age of 14 to 16 years leads to significantly more life-time savings, more or prolonged reduction of comorbidity and more QALYs gained.

Only a small percentage of potentially eligible adult subjects will ever undergo a bariatric procedure (26). The reason as to why is multifactorial and includes (amongst

others) costs, availability and fear of complications. Bariatric surgical procedures such as laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) (27, 28) modify gastrointestinal anatomy and physiology, require life long medical surveillance and are associated with a considerable amount of complications and long-term adverse effects such as GERD, chronic vomiting, dumping syndrome and nutritional deficiencies. New, minimally invasive or completely reversible procedures like the ACE stapler and gastric electrical stimulation (in an improved form) can possibly solve these problems and provide a solution for those who are now excluded from bariatric surgery. Even if it is difficult to reach the same amount of weight loss with these procedures when compared to traditional invasive procedures, we should continue to develop and study them, because if the results get close enough, with the current safety profile there is an enormous population to benefit from them.

Finally, although we usually don't say this part out loud, bariatric surgery is currently a profitable treatment for health care providers in the Netherlands. Recently, a Dutch hospital was declared bankrupt and one of their only profitable activities was the bariatric surgery department. Several hospitals battled against each other to be allowed to acquire their assets and staff. New indications for bariatric surgery (e.g. in adolescents) or new minimal invasive methods with low complication rates offer an opportunity for additional income at relatively limited costs for specialized health care providers.

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List of Publications

G.F. Paulus, M. van Avesaat, M. Westerterp-Plantenga, L.W.E. van Heurn, A.A.M. Masclee, N.D. Bouvy. Endoscopic gastroplication for morbid obesity. Effects on reduction of food intake and hormone profile after 1 year of follow-up. Submitted.

A. Talib, Y.G.M. Roebroek, **G.F. Paulus**, K. Van Loo, B. Winkens, N.D. Bouvy. L.W.E. van Heurn. Left Ventricular Geometrical Changes in Severely Obese Adolescents: Prevalence, Determinants, and Clinical Implications. Pediatric Cardiology. 2020 Oct 20. PMID: 33079265

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Dankwoord

DANKWOORD

Het is zover, het dankwoord. Ik moet bekennen dat ik dit afsluitende onderdeel van mijn proefschrift ongeveer 5 jaar geleden gepland had. Toen wist ik echter nog niet dat ik zo tevreden zou zijn over het eindresultaat, dat ik Limburg zou inruilen voor Amsterdam, dat ik daar een prachtig gezin op zou bouwen en ik wist ook nog niet zeker of ze me zouden willen hebben bij de chirurgie in de VU. Ik piekte dus wat later, waardoor de curve wat is afgevlakt. Dat schijnt veiliger te zijn en dan raakt het hele systeem niet overbelast. Mijn 'reguliere zorg' kon doorgaan.

Dit laatst-geschreven hoofdstuk is vaak het eerst-gelezen hoofdstuk wanneer een proefschrift op de deurmat valt en soms zelfs het enige. Ik ga mijn best doen om niemand te vergeten.

Allereerst wil ik alle patiënten bedanken die hebben meegewerkt aan mijn studies. Het is een grote eer om het vertrouwen te krijgen van mensen die al jaren met een probleem kampen (maar soms nog heel jong zijn) en een experimentele behandeling toe te mogen toepassen. Door intensieve testdagen die wel 24 uur konden duren en regelmatige controles bouwden we een sterke band op. Hoewel ik weet dat iedereen in goede handen achterbleef bij mijn opvolgers is het jammer dat ik jullie niet mee kon nemen naar Amsterdam.

Ik belandde bij kinderchirurgie in Maastricht na een zeer aanstekelijk sollicitatiegesprek met kinderchirurg Bas Verhoeven. **Bas**, inmiddels (terecht) regionaal opleider van de heelkunde opleiding in Nijmegen. Je bent een voorbeeld voor me als mens en als dokter. Ik leerde jou en je gezin beter kennen tijdens een congres in Barcelona (Pien: mijn beentjes zijn erg kort, kan iemand mijn koffer dragen?) en mocht af en toe bij je thuis op de koffie komen in 'ons' Roermond. Je oprechte interesse, je coaching en je openheid over eigen ervaringen zijn ongekend.

Als semi-arts kinderchirurgie kwam ik onder de vleugels terecht van Prof. dr. van Heurn. Beste **Ernst**, het duurde wat langer voordat ik jou kon doorgronden. Ik keek op tegen je enorme hoeveelheid kennis, ervaring en publicaties en voelde me dan ook vereerd dat je mij uiteindelijk een promotietraject aanbood. Je vroeg me wat ik wilde worden maar ik kon mezelf nog niet helemaal plaatsen tussen al die grote chirurgen. In een vaderlijk gesprek wist je mij te overtuigen gewoon het vak te kiezen dat ik het leukst vond. En zo begon mijn promotietraject. In die tijd heb ik je leren kennen als en gedreven en toegewijde promotor. Je hebt (of maakt) altijd tijd voor me en onze gesprekken duurden vaak een uur langer dan essentieel was voor de voortgang van het onderzoek. Ik wil je bedanken voor alle vrijheid die je me gegeven hebt om 'zelfrijzend bakmeel' te zijn. Het heeft zeker langer geduurd dan ik je beloofd had, maar het resultaat mag

er zijn en er gaan nog een paar huzarenstukjes verschijnen. Inmiddels zijn we beiden in Amsterdam beland en mag ik ook hier weer je leerling zijn bij de kinderchirurgie.

Het project waarmee ik startte was de BASIC trial, mijn 'kindje'. Het protocol was grotendeels geschreven maar ik mocht er mijn eigen draai aan geven en samenwerkingen smeden. Dat zijn er veel (heel veel) geworden. **Jan Willem** Greve, **Edgar** van Mil, **Anita** Vreugdenhil, **Coen** Stehouwer en **Chantal** Nederkoorn. Jullie waren er vanaf het eerste uur bij. Dank voor jullie hulp bij het ontwikkelen van het onderzoeksprotocol en jullie inzet van kennis, tijd en middelen. Al snel werd de onderzoekgroep uitgebreid met vakkennis vanuit (en van buiten) de hele organisatie. **Boudewijn** Brans, **Francois** van Dielen (bedankt dat je uit Eindhoven kwam invliegen om bij ons te opereren), **Bram** Felius (Leiden), **Boy** Houben, **Yvo** Kusters, **Jos** op 't Roodt (als ik aan jou denk hoor ik Gorki), **Kristien** van Loo, **Liesbeth** van der Ploeg, **Linda** Hover, **Luuke** Curvers, **Ida** Holterman, **Jesse** Rijks, **Simon** Robben, **Ruud** Severeijns, **Gerdy** Konings (nu jij nog!) en **Bjorn** Winkens completeren de basis van het onderzoeksteam. Dank voor jullie bereidheid om te sparren en voor jullie flexibiliteit wanneer afspraken in strakke schema's geperst moesten worden.

Al deze afspraken hadden nooit plaats kunnen vinden zonder 'de dames' van de heelkunde poli. Ik had altijd op de lastigste momenten plek nodig op de poli en spullen voor het onderzoek. Jullie zorgden er altijd voor dat het goed kwam. **Bernadette**, **Monique**, **Mylene**, **Annemarie**, **Christel**, **Ilma**, **Iris**, **Marion**, **Petra** en **Tanja**: jullie zijn onmisbaar, heel veel dank.

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Prof. dr. Bouvy, beste **Nicole**. Jij had onmiddellijk door dat er best nog wel wat vrije momenten waren tijdens het opzetten en draaiende houden van de BASIC trial. Soms hadden we geen patiënten, soms mochten we even niet door van de inspectie en anders kon het er wel naast. Je liet me meedoen bij je ambitieuze projecten waardoor mijn proefschrift volledig vorm begon te krijgen. Dat was af en toe rennen, maar er stond een heleboel tegenover. Je liet me deelnemen aan talloze (internationale) congressen waar ik mocht presenteren, netwerken, vrienden maken en waar ik zelfs op olympische sneeuw heb kunnen snowboarden. Ik heb erg veel waardering voor de manier waarop jij mensen weet te motiveren en hoe je voor iedereen kansen creëert.

Mark ("lange"). Doordat onze promotoren een gezamenlijk project hadden bedacht, begon onze samenwerking. Hoewel onze karakters wellicht op het oog wat verschillen klikte het meteen. Jij verplicht iedereen om je heen die de taal beheerst Limburgs te praten en daarmee was het ijs snel gebroken. Ik kwam erachter dat MDL-artsen

chirurgische internisten zijn waarmee je fantastisch kunt samenwerken én kunt feesten. De testdagen waren gezellig, we wisten alle noodvoorraden droogijs te vinden en we schreven samen beter dan alleen. De congressen die we bezochten waren een groot succes (je noemde zelf al Cacao Beach en 24h Miami, maar vergeet ons rood-velourse appartement in Sofia niet) en zo ben je een vriend voor me geworden. Ik ben je nog altijd dankbaar dat ik jullie huis mocht gebruiken toen ik er zelf even geen had. Ontzettend jammer dat de afstand tussen Amsterdam en Maastricht zo groot blijkt te zijn.

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Door deze ingang bij de MDL ontstonden nog een aantal vriendschappen. In iets varierende samenstelling bekend als het Melt!-, Lowlands-, vriendenweekend- of DWDD reünie-clubje; wat een onvergetelijke momenten met jullie: **Chantal** (Chanti), **Zlatan** (dr V.), **Marlou**, **Fedde**, **Britt**, **Dennis**, **Gwenny**, **Job**, **Mandy**, **Yvette**, **Joep**, **Corinne**, **Maarten**, **Ray-Michelle**, **Thomas**, **Bas** en tenslotte **Bouke** (Bou) en **Janneke** (Jans). Jullie hebben me zelfs 8 weken in huis genomen toen ik de laatste periode in Maastricht studies aan het afronden was. Ik kijk er naar uit deze clubjes weer volop leven in te blazen als de omstandigheden het toelaten. Daar bleef de samenwerking met MDL niet bij. Prof. dr. Fockens, beste **Paul**, bedankt voor de nuttige dag op het proefdierenlab en mijn eerste publicatie. **Tessa**, ook dankzij jou!

Nu heb ik mijn 'eigen' chirurgische club nog niet eens genoemd. Het lab: samengesteld uit 'passanten' zoals ik die een aantal jaren samen een avontuur beleven en een harde kern aan wetenschappers die niet weg te denken zijn en ons allemaal hebben geholpen onze tijd in goede banen te leiden. Ik heb een ontzettend mooie tijd gehad met de nodige koffie-momenten, borrels, WK-voetbal avonden, teamuitjes, etentjes en zelfs concerten. **Tiara**, **Martine** en **Lori**, mijn roommates. Muziek speelde een altijd belangrijke rol op onze kamer en werd zelden onderbroken voor iets anders. **Joyce-Manji** (altijd in voor een feestje), **Anne-Claire** (wervelwind, altijd lachen), **Selwyn** (thanks voor je support toen je als referent gebeld werd), **David**, **Frans**, **Tim**, **Jasper**, **Dirk**, **Kostan** (jij moest Pien's koffer dragen), **Toine**, **Irene-Fleur**, **Kim**, **Inca**, **Ruben**, **Edgar**, **Victor** (mooi dat we nu samen hier in opleiding zijn!), **Liliane**, **Dennis**, **Jungfang**, **Kiran**, **Bas**, **Mo** (onmisbaar onderdeel van het interieur), **Sander**, **Kaatje** en **Livia**. En niet te vergeten mijn studenten **Loes**, **Dick**, **Susan** en **Jasper**. Het was leuk jullie te begeleiden!

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Curriculum Vitae

Givan Florian Paulus was born on the 19th of June 1984 in Roermond, the Netherlands. He is the eldest of four children born to Walter Paulus and Corry van Eck. After finishing secondary sachool at BC Schöndeln (Roermond) in 2003, he studied Mechanical Engineering (Eindhoven) for a short period, only to discover that his heart lay elsewhere. In 2004 he started medical school at the Maastricht University Faculty of Health, Medicine and Life Sciences. After obtaining his medical degree he followed an MD-PhD program at the General Surgery department of the Maastricht University Medical Center+, under supervision of Prof. dr. Ernst van Heurn and Prof. dr. Nicole Bouvy. The research was performed at de department of Human Biology, part of NUTRIM School of Nutrition and Translational Research in Metabolism (Maastricht University). In 2015 he started his clinical career at the General Surgery department of the Spaarne Gasthuis (Haarlem). Since 2017 he has been a surgical resident in the VU University Medical Center region (Amsterdam) under supervision of dr. Herman Rijna, dr. Steven Oosterling and Prof. dr. Donald van der Peet. He currently lives in Amsterdam with Anja and their two children Mila and Mats.