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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I–III):

I Sillakivi T, Suumann J, Kirsimägi U, Peetsalu A. Plasma levels of gastric biomarkers in patients after bariatric surgery: biomarker after bariatric surgery. Hepatogastroenterology. 2013 Nov-Dec;60(128):2129–32.

II Suumann J, Sillakivi T, Riispere Ž, Syrjänen K, Sipponen P, Kirsimägi Ü, Peetsalu A. Serological biomarker testing helps avoiding unnecessary endoscopies in obese patients before bariatric surgery. BMC Obes. 2018 Feb 20;5:9.

III Suumann J, Sillakivi T, Riispere Ž, Syrjänen K, Sipponen P, Kirsimägi Ü, Peetsalu A. Serum gastric biomarker levels after sleeve gastrectomy and Roux-en-Y gastric bypass operations: a prospective study with 1-year follow-up. Surgery Gastroenterology and Oncology. 2019 Apr 24(2):86

Author's contribution:
Involvement in the study design, in patients' recruitment and follow-up, in collecting clinical data, in participating in majority of the operations, and in writing of the text of the manuscripts.

ABBREVIATIONS

AG	atrophic gastritis (mucosal atrophy)
AGA	atrophic gastritis of the antrum
AGC	atrophic gastritis of the corpus
AGP	atrophic pan-gastritis (AG of the antrum and corpus)
BMI	body mass index
EGDS	esophagogastroduodenoscopy
%EWL	percentage of excess weight loss
GERD	gastroesophageal reflux disease
G17b(f)	basal (fasting) Gastrin 17
G17s	stimulated amidated Gastrin 17
GP	GastroPanel
HPAB	Helicobacter pylori antibodies
HP	Helicobacter pylori
HS	healthy stomach
LA	Los Angeles classification of esophagitis
LRYGB	laparoscopic Roux-en-Y gastric bypass
LSG	laparoscopic Sleeve Gastrectomy
NHS	non-healthy stomach
PgI	Pepsinogen I
PgII	Pepsinogen II
RYGB	Roux-en-Y gastric bypass
SG	Sleeve Gastrectomy
USS	updated Sydney System

1. INTRODUCTION

The prevalence of overweight and obesity has increased over several decades becoming an increased health risk in modern society both in developed and developing countries. Nowadays it has become priority in healthcare all over the world [Ogden et al., 2006; Benotti et al., 1995; Williams et al., 2015; Kelly et al., 2013]. According to the World Health Organization, in 2016 more than 1.9 billion adults 18 years of age and older were overweight. Of these over 650 million were obese [WHO, 2021].

Overweight and obesity are risk factors for gastroesophageal reflux disease, erosive esophagitis, hiatal hernia, Barret's esophagus, esophageal adenocarcinoma, Helicobacter pylori infection. Most of these conditions are observed up to 2–3 times more frequently in obese patients than in normal weight persons [Gerson LB., 2009].

In parallel to the growth of obese people, the number of bariatric operations has also increased, since it is the the only effective way to treat obesity, resulting in sustainable and significant weight loss in the long term (along with the resolution of metabolic comorbidities in up to 80% of cases) [Flum et al., 2007 ; Azagury et al., 2011].

Operations on the stomach alter more or less the gastric mucosa and gastric secretory functions in gastric remnants, as was shown earlier after gastric vagotomies or partial gastric resections in peptic ulcer cases [Peetsalu et al., 1990]. However, information about these changes and association with postoperative morbidity in the bariatric cohort is limited.

Upper digestive endoscopy with gastrobiopsies has been the gold standard in pre– and postoperative investigation of bariatric patients to evaluate the state of the stomach and to detect possible abnormalities. Nevertheless, the value of and the need for routine endoscopy in asymptomatic patients remains controversial [Parikh et al., 2016; Csendes et al., 2007; D`Hondt et al., 2013; Almazeedi et al., 2013; Gerson LB., 2009].

During past decades, the use of serological biomarker testing ("serological biopsy") has gained increasing popularity as a non-invasive diagnostic tool for dyspeptic patients and asymptomatic subjects to diagnose both functional disorders and gastric diseases, including Helicobacter pylori (HP) infection and mucosal atrophy (AG) [Agreus et al., 2012]. The latest innovation in this technology represents a panel of 4 stomach-specific biomarkers (Pepsinogen I and II, Gastrin-17 and HP antibody) (PgI, PgII, G-17, HPAP) known as GastroPanel® (GP) test, which distinguishes between 8 diagnostic marker profiles [Agreus et al., 2012; Syrjänen et al. 2019].

The knowledge of alterations in stomach physiology after bariatric surgery is an important clinical issue. The sequelae caused by resections or bypasses are persistent and will remain and act over many postoperative years or even decades. Since the number of bariatric operations is growing worldwide, the possibility to evaluate the "health" of gastric mucosa pre- and postoperatively,

using noninvasive methods, would be very attractive, especially in patients after (mini) gastric bypass operation.

In our studies we aimed to find out if serologigal biomarker testing could avoid invasive endoscopies in obese patients undergoing for bariatric surgery and to characterize the gastric biomarker profile and its dynamics after sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). Identifying changes in the gastric biomarker profile could provide important new information about possible complications and complaints after bariatric surgery, as well as could help to institute individualised therapy, including replacement therapy, after specific types of bariatric operation.

2. REVIEW OF THE LITERATURE

2.1. Definition of overweight and obesity

The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health [WHO, 2021]. Body mass index (BMI), calculated by dividing body weight in kilograms by the square of height in meters, is a simple metric used to indicate overall body fatness [WHO, 2021]. For adults, current guidelines from the US Centers for Disease Control and Prevention (CDC) and the WHO define a normal BMI range as 18.5 to 24.9, whereas a BMI of ≥25 kg/m^2 is considered to be overweight, and a BMI of ≥30 kg/m^2 is classified as obese, with severe obesity defined as a BMI of ≥40 kg/m^2. For children, age needs to be considered when defining overweight and obesity [WHO, 2021; Chooi et al., 2019].

2.2. Prevalence of overweight and obesity

According to WHO, in 2016, 39% (1.9 billion) adults aged 18 years and older (39% of men and 40% of women) were overweight and about 13% (650 million) of the world`s adult popu-lation (11% of men and 15% of women) were obese. Overweight and obesity are serious problems among children: in 2016, over 340 million children and adolescents aged 5–19 were overweight or obese. In 2019, an estimated 38.2 million children under the age of 5 years were overweight or obese [WHO, 2021]. The data published in 2015 by Ogden and colleagues showed that more than one-third of adults and 17% of adolescents in the United States were obese in 2011–2015 [Ogden et al., 2015]. According to the data from the National Institute for Health Developement, 32.4% of adults (aged 16–64) were overweight and 20% obese in Estonia in 2020 [TAI, 2021]. Of the adolescent population (aged 11–15), 17.1% were overweight/obese in 2018 [TAI, 2019].

2.3. The burden of obesity

Obesity represents a major health challenge because it substantially increases the risk of the diseases such as type 2 diabetes mellitus (T2DM), fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnoea and several cancers, thereby contributing to a decline in both quality of life and life expectancy. Obesity is also associated with unemployment, social disadvantages and reduced socio-economic productivity, thus increasingly creating an economic burden [Blüher et al., 2019].

In 2016 the total cost of chronic diseases due to obesity and overweight in the U.S. was $1.72 trillion− equivalent to 9.3 percent of the U.S. gross domestic product (GDP) [Waters et al 2018].

Importantly, the World Obesity Federation and other organizations, including the American and Canadian Medical Associations, have declared

obesity a chronic progressive disease clearly distinct from being just a risk factor for other diseases [Bray et al., 2017].

Reducing the obesity-related burden to health and societies as well as reversing the increase in obesity prevalence is a high priority for the WHO, which included the target to halt obesity prevalence at the level it was in 2010 as one of the main targets of the 'Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020` [WHO, 2021].

2.4. Possible causes of obesity

The fundamental cause of obesity is a long-term energy imbalance between too many calories consumed and too few calories expended. Global estimates, based on food balance sheets, indicate that the available per capita food in developed countries was 3138 kcal/person/day in 1969/1971 and 3360 kcal/person/day between 2005 and 2007. In developing countries, the per capita food available increased from 2055 to 2619 kcal/person/day during the same three and a half decades [Alexandratos et al., 2012].

Although obesity prevalence increased in every single country in the world, regional differences exist in both obesity prevalence and its trends. Changes in the global food system together with increased sedentary behaviour seem to be the main drivers for the obesity pandemic [Blüher, 2019].

Most areas of the world have shown economic development that has resulted in increased purchasing power which is an important factor in explaining the increasing caloric intake [Gerbens-Leenes et al., 2010].

A study by Vandevijvere et al. found that a higher energy intake was sufficient to explain the increasing population body weight, especially in high-income countries [Vandevijvere et al., 2015].

Biological factors play also a role in the pathogenesis of obesity. The key role of certain brain regions in the regulation of body weight became evident from observations that animals with lesions and humans with tumours, affecting the hypothalamus, develop abnormal food-seeking behaviour and obesity [Farooqi, 2014].

A mutation in the *ob* gene (which encodes the adipose tissue hormone leptin) causes severe obesity in *ob/ob* mice, therefore it became apparent that the central neural circuits that control energy homeostasis integrate signals from peripheral tissues such as the adipose tissue [Zhang et al. 1994; Coleman et al., 1969; Farooqi et al., 2014]. Mutations in the genes coding for leptin, leptin receptor, melanocortin 4 receptor, pro-opiomelanocortin and others might cause severe obesity in humans, which underlines the importance of biological factors in the pathogenesis of obesity [Montague et al., 1997; Clément et al., 1998]. As monogenetic mutations are rare, changes in population genetics cannot explain the rise in obesity prevalence in just 40 years.

Individual factors (such as the genetic background or the gut–brain–hormone axis) influence susceptibility to obesity, which may develop in an obesogenic environment (for example, influenced by eating culture, transportation and

computerization). Obesity is not caused by personal choice or by society, but rather by the relationship between an individual and their environment [Blüher, 2019]. Obesity is the result of the interplay between heterogenic factors, deriving from a person's eating behaviour, physical activity and individual energy expenditure determinants [Butland et al., 2007].

Several studies have demonstrated differences in the microbiome composition of obese, overweight, and lean individuals [Turnbaugh et al. 2009]. Although the exact mechanisms of the action of gut microbes on obesity are not fully known, the diversity of microorganisms in the human gastrointestinal tract is very important. Gut microbes (microbiota) may influence human/host body weight in several ways: promoting increased fat storage in the adipose tissue, processing indigestible luminal polysaccharides into short chain fatty acids, influencing the absorbtsion of nutrients and production of hormones (ghrelin, leptin, glycagon-like peptide-1 (GLP-1)) [Mulla et al. 2018]. In an experiment scientists collected the fecal microbiota from identic adult female twin pairs discordant for obesity and transplanted it into a germ-free mice gastrointestinal tract. The mice harboring the obese twin`s microbiota became/turned obese, but the mice harboring the lean co-twin`s microbiota did not [Ridaura et al. 2013].

Bile acids also play an important role in body weight regulation being mediators of intestinal absorption of lipophilic nutrients. They are also considered mediators of systemic metabolism, serving as ligands for farnesoide X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). In the gut lumen they can regulate the production of incretin hormones, such as GLP-1. Bile acids also influence the microbiome through the antimicobial properties of conjugated bile species. Bile acids can increase the ciruclating levels of fibroblast growth factor-19 (FGF-19) in the postprandial state, which in turn regulates glycose and lipid metabolism, as well as bile acid synthesis. The plasma levels of both primary and secondary bile acids are increased after laparoscopic gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) [Mulla et al. 2018].

2.5. Treatment of obesity

2.5.1. Lifestyle interventions

Lifestyle and behavioural interventions aimed at reducing calorie intake and increasing energy expenditure have limited effectiveness, because complex and persistent hormonal, metabolic and neurochemical adaptations defend against weight loss and promote weight regain [Blüher, 2019]. Speakman et al. demonstrated that the energetic balance is regulated in a way to maintain the target value („set point"). Discrepancies between the level of the signal and the target are translated into effects on energy expenditure and energy intake to equalise the discrepancy and maintain homeostasis [Speakman et al., 2011].

Studies on lifestyle interventions in the treatment of obesity usually have a short observation period (1–2 years) and show a modest effect on weight loss. Weight regain is common after the conclusion of a lifestyle intervention, as

observed in a study by Foster et al. [Foster et al., 2010]. Wadden et al. demonstrated that with no further treatment patients typically regain one third of lost weight in the first follow-up year, with continuing weight gain thereafter, and return to their baseline weight within 4–5 years. About half of patients receive additional weight compared to baseline weight [Wadden et al., 1989].

2.5.2. Medical therapy

The panoply of available medications for weight loss has evolved significantly in the last half century. The Food and Drug Administration (FDA) has approved weight loss medications dating back to 1959 for short-term (<12 weeks) use. With increased recognition of obesity as a chronic, complex medical disease, newer agents have been approved as long-term therapy, and the cornerstone of treatment is chronic behavior and lifestyle change [Velazguez et al., 2018].

As indicated in the 2015 Endocrine Society Clinical Practice Guidelines on Pharmacologic Management of Obesity, all patients with a body mass index (BMI) >25 kg/m^2 warrant intervention with diet, exercise, and behavior modification. Weight loss medications should be introduced as adjuncts to diet, exercise, and behavioral modification for patients with a BMI >30 kg/m2 or patients with a BMI >27 kg/m2, if they have at least one obesity related comorbid condition, such as T2DM, dyslipidaemia, hypertension, sleep apnea. The objective of using pharmacotherapy in management of obesity is to amplify patient adherence to lifestyle changes and to overcome the biological adaptations that occur with weight loss. Most anti-obesity drugs have an efficacy of 3–7% (estimated net weight loss). The usage of these medications is limited because of their adverse effects [Apovian et al. 2015; Srivastava et al., 2018].

Major FDA-approved anti-obesity medications are: Phentermine, Orlistat, Phentermine/topiramate extended release (ER), Naltrexone sustained release (SR)/bupropion sustained release (SR), Liraglutide and Semaglutide. Phentermine is a noradrenergic drug that acts on the sympathetic nervous system, causing an increase in norepinephrine release. This neurotransmitter release leads to appetite suppression in addition to increased resting energy expenditure (Rothman et al. 2001]. Orlistat inhibits the activity of pancreatic and gastric lipasis, thereby decreasing fat absorbtion by 30%. Orlistat is indicated for weight loss in conjunction with a reduced-calorie diet [Tak et al., 2021; Apovian et al., 2016]. Phentermine/topiramate ER is the first combination medication approved for chronic management of obesity. Topiramate ER acts on GABA receptors, leading to appetite suppression. The combination drug has shown greater potential weightloss effects than monotherapy alone for each, while also reducing adverse effects [Tak et al., 2021; Apovian et al., 2016]. Naltrexone SR/bupropion SR− the mechanism of action for buproprion SR is inhibition of dopamine and norepinephrine reuptake. Naltrexone acts to antagonize the feedback loop that limits buproprion's anorexic effects; hence, this drug combination works synergistically [Greenway et al., 2009]. Liraglutide and semaglutide are analogs of human glucagon-like peptide-1 (GLP-1)

with a much longer half-life of 13 h compared with the human endogenous GLP-1 that lasts only a few minutes. These drugs mimic the actions of endogenous GLP-1, a hormone released from the small intestine, which plays a role in the peripheral regulation of appetite through anorexigenic effects in addition to effects of increasing release of insulin from the pancreas in the presence of glucose [van Can *et al.* 2014].

The latest studies with semaglutide (analog of human GLP-1) have shown promising results in weight loss. In a systematic literature review with meta-analysis Smith et al., demonstrated that semaglutide 2.4 mg weekly is associated with a greater weight change from baseline (>5%) compared to pharmacolocical comparators for weight management in overweight or obesity [Smith et al., 2022].

Comparative studies of medical treatment versus surgery are still in progress and long-term results are not known yet.

2.5.3. Surgery for obesity

2.5.3.1. Indications for bariatric surgery

Bariatric surgery is indicated to patients older than 18 years having the following characteristics:

- BMI ≥40 kg/m^2
- BMI 35–40 kg/m^2 with co-morbidities in which surgically induced weight loss is expected to improve the disorder (such as metabolic disorders, cardiovascular diseases (myocardial infarction, stroke), respiratory diseases (chronic obstructive pulmonary disease, sleep apnea), severe ostoearthritis, obesity related severe psychological problems, polycystic ovarian syndrome).
- Patients with BMI >30<35 kg/m^2 with T2DM may be considered for bariatric surgery on an individual basis, as there is evidence-based data supporting bariatric surgery benefits in regard to T2DM remission or improvement [Fried et al., 2014; Di Lorenzo et al. 2020].

The above mentioned indications, which have been used for almost 30 years (with minor changes), are currently under adjustment, as the new guidelines of the American Society for Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and MetabolicDisorders (IFSO) 2022 were released. These new guidelines will increase the proportion of people eligible for bariatric surgery [Eisenberg et al., 2022].

2.5.3.2. Bariatric surgical procedures

In parallel to the growth of obese people, the number of bariatric operations has also increased, since it is the the only effective way to treat obesity in the long term. A variety of surgical options are currently offered for treatment of obesity. The beginning of the third millennium has seen constant evolution of invasive techniques, such as laparoscopy and flexible transoral endoscopy [Lee, 2017].

According to the IFSO survey, the total number of primary bariatric operations performed in 2016 was 609,897 worldwide. The most frequently performed surgical bariatric/metabolic procedure was sleeve gastrectomy (SG) (N=340,550), followed by Roux-en-Y gastric bypass (RYGB) (N=191,326), One-Anastomosis Gastric Bypass (OAGB) (N=30,563), Adjustable Gastric Banding (AGB) (N=19,332) and Biliopancreatic Diversion/Duodenal Switch (BPD/DS) (N= 3346) [Angrisani et al., 2018] **(Figure 1)**.

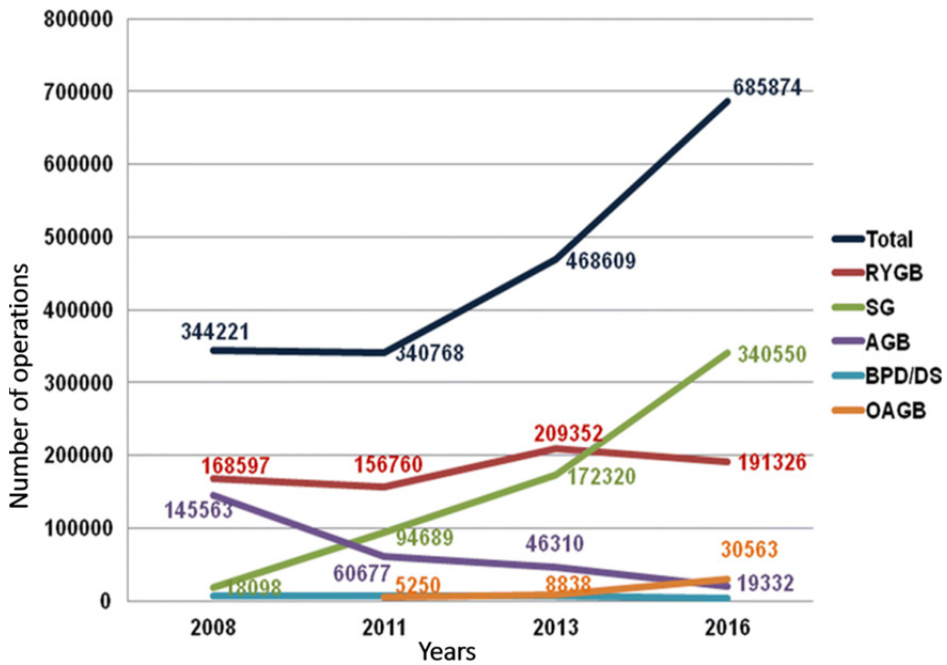


Figure 1. Number of main primary bariatric/metabolic surgical procedures from 2008 to 2016 worldwide. AGB adjustable gastric banding, RYGB Roux-en-Y gastric bypass, SG sleeve gastrectomy, BPD-DS biliopancreatic diversion-duodenal switch, OAGB one-anastomosis gastric bypass [Angrisani et al., 2018] (Reproduced with the permission of Springer Nature)

The first bariatric operation in Estonia (adjustable gastric banding) was performed at the North Estonia Medical Center in 2004, since then their number has increased **(Figure 2)**. In 2021 there were 757 bariatric operations (569 operations per one million inhabitants), the two most favored type operations being RYGB (N=323) and SG (N=219). In 2022 the total number was 1,074 [EBMKS, 2023] **(Figure 2, 3)**. The total number of bariatric/metabolic procedures performed in Estonia between 2004 and 2022 was 9,197 **(Figure 2)**.

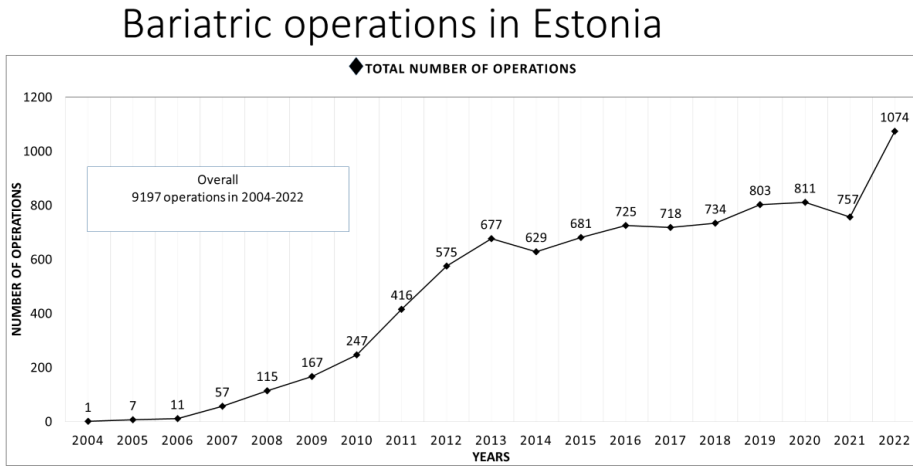


Figure 2. Number of bariatric operations in Estonia in 2004–2022 [EBMKS, 2023]

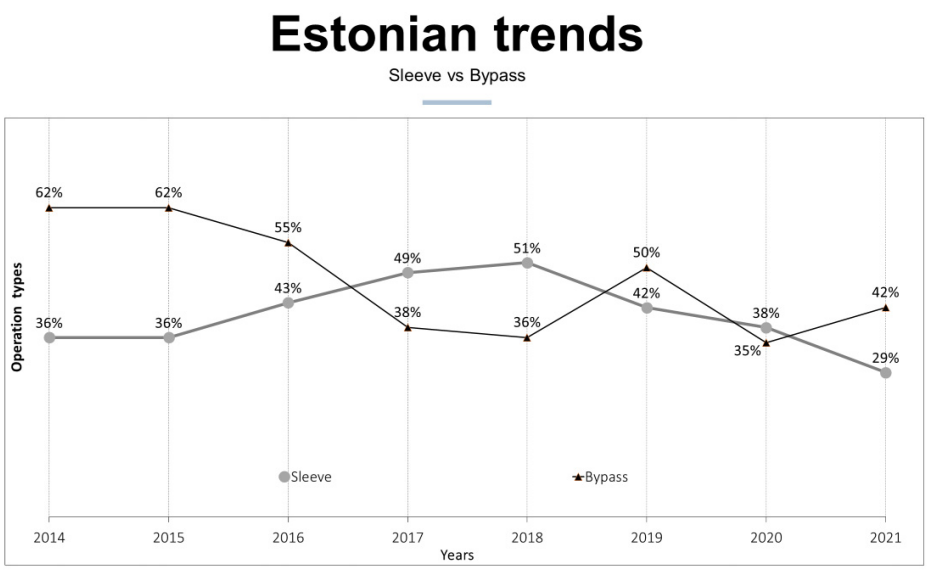


Figure 3. Bariatric/metabolic surgical procedures in Estonia in 2004–2021. Sleeve – Sleeve gastrectomy; Bypass – Roux-en-Y gastric bypass [EBMKS, 2023]

Sleeve gastrectomy (SG).

SG was performed for the first time in 1988 as part of the biliopancreatic diversion with duodenal switch (BPD-DS). SG is a restrictive type bariatric operation where most of the corpus and antrum is resected and removed to create a long, tubular gastric conduit along the lesser curve of the stomach

(Figure 4A). It was first used in a two-staged approach in an attempt to reduce surgical risk in superobese patients with SG as the first stage. Since 2007 SG has been used as a primary bariatric procedure. The main strengths of SG are the low rate of complications, short operative time, absence of foreign material, lack of gastrointestinal anastomosis and malabsorption, patient's acceptance, and feasibility to be converted to multiple other bariatric procedures [Angrisani et al., 2018].

Roux-en-Y gastric bypass (RYGB).

Laparotomic Roux-en-Y gastric bypass (RYGB) was described for the treatment of morbid obesity in 1966 by Mason and Ito, who proposed it for treating morbid obesity. It is a combined (restrictive and malabsorbtive) method where by separating the upper part of the stomach a new smaller stomach (pouch) is created. The small intestine is divided and one end is anastomosed to the pouch. A second anastomosis is made to connect the disconnected stomach and duodenum to the small bowel. This connection enables the digestive fluids to meet ingested food enabling nutrient breakdown and absorption. The distance between the two connections can vary, but is generally 50 to 150 cm. Laparoscopic RYGB was first described by Wittgrove et al. in 1994**.** It was the most popular type bariatric operation for decades and is still considered by many as the gold standard [Angrisani et al., 2018] **(Figure 4B)**.

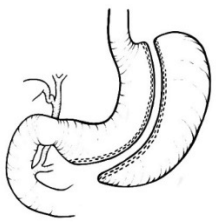
Biliopancreatic Diversion-Duodenal Switch (BPD-DS).

Biliopancreatic diversion was described by Scopinaro in 1976. This procedure consists in a horizontal distal gastrectomy with a proximal gastric pouch with closure of the duodenal stump, a gastroileostomy, with a 250-cm limb of the distal ileum, and a biliopancreatic limb anastomosed to the distal ileum, creating a 50-cm common channel. In 1988 Hess modified BPD to BPD-DS where the most important changes involved use of vertical gastrectomy and division of the duodenum between the pyloric valve and the sphincter of Oddi **(Figure 4C)**. Deriving from experience with BPD, BPD-DS has a longer common channel to reduce the likelihood of vitamin, mineral, and protein deficiencies. The first laparoscopic BPD-DS was performed in 1999 [Angrisani et al., 2018].

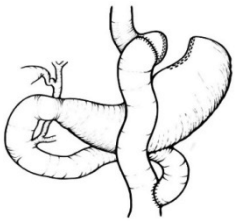
One-Anastomosis Gastric Bypass (OAGB).

OAGB was first reported in 2001 by Rutledge. It is a a combined (restrictive and malabsorbtive) method performed with the laparoscopic technique. During the OAGB procedure, the surgeon first reduces the size of the "working" stomach by separating a tube-like pouch of the stomach from the rest of the stomach. This tubular gastric pouch is then anastomosed to the intestine, bypassing up to 200cm of the upper part of the intestine. This technique differs from the traditional RYGB which requires two anastomoses [Angrisani et al., 2018] **(Figure 4D)**.

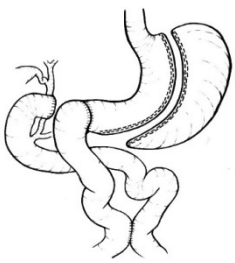
Adjustable gastric banding (AGB).
AGB is a restrictive type bariatric procedure first described by Kuzmak et al. in 1986. During the AGB procedure a silicone band (equipped with a firmly attached inflatable balloon) is placed around the upper part of the stomach, creating a 15- 30ml pouch. The size of the pouch outlet is adjusted by adjusting the volume of fluid in the balloon through the access port situated under the skin usually in the upper abdomen. The first band was placed laparoscopically in a human by Belachew and colleagues in September 1993 [Angrisani et al., 2018] **(Figure 4E)**.



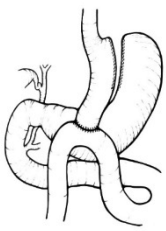
A Sleeve gastrectomy (SG)



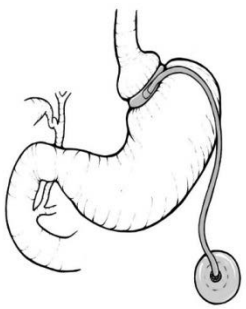
B Roux-en-Y gastric bypass (RYGB)



C Biliopancreatic Diversion-Duodenal Switch (BPD-DS)



D One Anastomosis Gastric Bypass (OAGB)



E Adjustable gastric banding (AGB)

Figure 4. Graphic depiction of bariatric surgery types (Figure by T. Veršinina)

2.5.3.3. Mechanisms of weight loss in bariatric operations

The mechanisms of bariatric operations contributing to weight loss can vary in the different type procedures, being often combined. These mechanisms include effects on regulation of energy balance, both central and peripheral nervous systems` regulation of appetite and metabolism, but also changes in gut hormones and microbioma [Mulla et al., 2018]. Bariatric surgery changes the secretion of gut hormones (incretines) which play a key role in regulating appetite, satiety, food intake, systemic metabolism, and insulin secretion [Campbell et al., 2013].

The most important gut hormones are:

- GLP-1 (glucagon-like peptide-1). This L-cell derived hormone increases glycose-dependent insulin secretion, inhibits clycagon secretion, confers glucose sensitivity to glucose-resistant β cells, stimulates β cell proliferation and neogenesis, and inhibits β cell apoptosis. GLP-1 analogues are effective therapeutics for human T2D and obesity. GLP-1 is increased after RYGP (in the fasting and postprandial states`) and LSG (in the postprandial state).
- PYY (Peptide YY). Secreted from L-cells of the distal small intestine and the colon. PYY levels are increased in the postprandial state after RYGB and LSG, and they act on reducing food intake.
- FGF-19 (fibroblast growth factor-19) – peptide hormone that regulates bile acid synthesis, as well as glucose and lipid metabolism.
- GIP (Glucose-dependent insulinotropic polypeptide) – peptid hormone secreted by K cells in the proximal small intestine. GIP signalling increases glucose dependent insulin secretion, postprandial glucagon secretion, and intestinal glucose absorbtion. GIP action in the adipose tissue promotes storage, with increased glucose uptake, conversion of clucose to fatty acids, and activation of lipoprotein lipase. Postprandial levels of GIP are reduced after RYGB.
- Ghreline – orexigenic hormone, produced in oxyntic glands in the gastric fundus. Its concentrations increase in the fasted state and decreases in the postprandial state. Ghrelin levels are suppressed following bariatric surgery in some studies.
- Oxyntomodulin – anorexigenic hormone that is increased after a glucose load. Its levels are high after RYGP [Mulla et al.,2018].

2.5.3.4. Selection of the operation method

Opting for the appropriate operation type for weight loss continues to be a challenging and subjective process. In experienced hands, most operations can be successful in providing a given patient with successful weight loss, amelioration of comorbidities and improvement in quality in life [Needleman et al. 2008]. Currently, laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are the most commonly performed bariatric procedures worldwide to treat obesity [Angrisani et al., 2021].

In a systematic review (5 RCT) of Colquitt et al., LRYGB had no superiority to LSG in the percentage of excess weight loss (%EWL) [Colquitt et al., 2014]. According to the study of Peterli et al. (SM-BOSS), there was no significant difference in excess BMI loss between LSG and LRYGB at 5-year follow-up (for LSG, 61.1%, vs LRYGB, 68.3% [Peterli et al. 2018]. Similar results were obtained in the SLEEVEPASS trial (the estimated mean %EWL at 10 years was 43.5% after sleeve gastrectomy and 50.7% after gastric bypass) [Salminen et al., 2022]. For superobese patients (BMI>50), biliopancreatic diversion with duodenal switch resulted in greater weight loss than RYGB (2RCT; P<0.001) [Colquitt et al., 2014].

Gastroesophageal reflux disease (GERD) can certainly be one of the key points in the decision making process. Although several studies [Pallati et al. 2014; Sucandy et al., 2015] have demonstrated improvement in GERD after LSG, some studies report the opposite [Melissas et al., 2015; Sheppard et al. 2015]. A recent study of Csendes et al. demonstrates „de novo“ GERD in 58.5% of patients (without reflux symptoms and normal endoscopy preoperatively), and worsening endoscopic parameters in patients with preoperative GERD symptoms 10 years after LSG [Csendes et al. 2019]. This is also supported by a paper of Genco et al., where the Barret mucosa is present in up to 17% of asyptomatic patients 5 years after LSG [Genco et al., 2017]. In a SM-BOSS study Peterli et al. demonstrate that GERD symptoms worsened more often after LSG than after LRYGB (31.8% vs 6.3%; P=0.006). In the same study de novo reflux symptoms occured in 31.6% of the LSG patients compared to 10.7% in the LRYGB group (P=0.01) [Peterli et al., 2018]. In a SLEEVE-PASS study the authors reported that at 10 years, esophagitis was more prevalent after LSG than after LRYGB (31% vs 7%; P <0.001) while the Barret esophagus was described in 4% of patients (in both groups) [Salminen et al., 2022].

According to the current conditional recommendations of the Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery, LSG should not be performed in patients with severe GERD symptoms and/or severe oesophagitis [Di Lorenzo et al., 2020].

2.5.3.5. Effectiveness of bariatric surgery

Effectiveness and durability are considered the key attributes of bariatric surgery when compared with the non-surgical approaches to achieving weight loss. During the past three decades, bariatric surgery has gained an increasingly important role in the management of the most severe cases of obesity, since it is practically the only effective and way to treat obesity, resulting in sustainable and significant weight loss in the long term (along with the resolution of metabolic comorbidities in up to 80% of cases), as well as in improving quality of life [O'Brien PE et al. 2019; Flum et al. 2007].

The effectiveness of bariatric surgery is often described by weight loss and/or with resolution of or improvement in obesity related diseases. Weight

loss is usually reported as the mean percentage of excess weight loss (%EWL), which is the standard in the bariatric surgery nomenclature. This calculation is derived from the formula: percentage of excess weight loss = (weight loss/excess weight) × 100, where excess weight = total preoperative weight – ideal weight. Changes in absolute weight (kilograms), BMI, and percentage of initial weight are also reported when appropriate.

In a meta-analysis of Buchwald et al., the effectiveness of bariatric surgery on weight loss and resolution of obesity related comorbidities was demonstrated in 22094 patients. The mean %EWL at the outcome time point for which the comorbidities were assessed was 47.5% (95% CI, 40.7%-54.2%) for gastric banding, 61.6% (56.7%-66.5%) for gastric bypass, 68.2% (61.5%-74.8%) for gastroplasty, and 70.1% (66.3%-73.9%) for biliopancreatic diversion or duodenal switch. Type 2 diabetes was completely resolved in 76.8% of patients and resolved or improved in 86.0%. Hyperlipidemia improved in 70% or more patients, hypertension was resolved in 61.7% of patients and resolved or improved in 78.5%. Obstructive sleep apnea was resolved in 85.7% of patients [Buchwald et al. 2004]. The results of a Swedish Obesity Subjects (SOS) study of Sjöström L., demonstrate good long term effects of weight loss surgery: mean changes in body weight after 2, 10, 15 and 20 years were −23%, −17%, −16% and −18% in the surgery group and 0%, 1%, −1% and −1% in the control group respectively. Compared with usual care, bariatric surgery was associated with long-term reduction in overall mortality and decreased incidences of diabetes, myocardial infarction, stroke and cancer [Sjöström, 2013]. In a systematic review (6 RCT) Colquitt et al. demonstrated that bariatric operations, regardless of the surgical intervention used, had better results in weight loss compared with no surgery at 1–10 years of follow-up ($p<0.001$). Resolution of comorbidities was also higher after surgery compared with conventional therapy [Colquitt et al., 2009]. In a systematic review O`Brien et al. published long-term outcomes of weight loss after 10 or more years following different bariatric operations. There were 18 reports on gastric bypass, 16 of which were for the RYGB variant and two were for the OAGB variant. All gastric bypasses combined showed a weighted mean % EWL of 56.7% at 10 or more years with a mean of 55.4% EWL for RYGB and 80.9% EWL for OAGB. The mean EWL for the 17 reports on laparososcopic adjustable gastric banding (LAGB) was 45.9%. For two RCTs with the use of LAGB, the mean weight loss was 55.9% EWL. Eleven reports on biliopancreatic diversion-duodenal switch (BPD ± DS) presented a mean of 74.1% EWL. In studies of BPD (N = 4), the weighted mean was 71.5% EWL, while for DS (N = 7), it was 75.2% EWL. Two reports on sleeve gastrectomy with a total of 79 patients presented a mean of 57.0% EWL [O`Brien et al. 2019].

2.5.3.6. Cost-effectiveness of surgical versus non-surgical treatment for obesity

The cost-effectiveness of bariatric surgery compared to non-surgical (NST) treatment has been discussed by many authors. Studies of Borisenko et al. demonstated that among German and Danish bariatric patients, bariatric surgery, compared to NST, was cost-effective at 10 years and over the lifetime. At 10 years the incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALYs) was EUR2457 in Germany and 17,818DKK in Denmark. Over the lifetime, surgery led to the saving EUR8522 and generated an increment of 0.7 years of life or 3.2 QALYs in Germany [Borisenko et al., 2017a,b]. The authors also showed that surgery may produce significant reduction in healthcare costs and a delay in surgery for up to 3 years may result in reduction in life years and QALYs gained [Borisenko et al., 2017a,b]. According to An et al., bariatric surgery was cost-effective (ICER of 674USD per QALY) compared to NST in Korean people with morbid obesity [An et al., 2020]. A study conducted by Gulliford et al, with obese 250, 000 patients demonstrated better outcomes of bariatric surgery compared to NST. In that sudy, bariatric surgery was associated with an increase in total life years of 6,097 per 1000 participants (accumulated over the lifetime of the participants), an increase in a number of life years, lived free from chronic comorbidities, of 10,297 per 1000 participants compared to NST. Although according to the study, bariatric surgery was not cost-saving, the increased healthcare costs were exceeded by the health benefits to obese individuals [Gulliford et al 2017].

2.6. Complications of bariatric surgery

2.6.1. Surgical complications

Bariatric surgery procedures are safe and carry a low risk of complications, especially in the setting of specialized centers. The avarage rate of complications in bariatric surgery is less than 10% [Sjöström et al., 2004] and overall mortality rate is <1% in most published series, with lower-risk patients showing a mortality rate of <0.35% (similar to that for cholecystectomy) [Dumon et al., 2011]. Buchwald and colleagues reported a 0.28% of early (less than 30 day) and 0.35% of late (30 days to 2 years) mortality rate after bariatric surgery in 85,048 patients [Buchwald et al., 2007]. The Swedish Obesity Study reported a mortality of 0.25% within 90 days of surgery [Sjöström et al., 2007].

Some complications can be procedure-specific. The most frequently reported perioperative complications associated with LRYGB are wound infection (2.98%), anastomotic leak (2.05%), gastrointestinal tract hemorrhage (1.93%), bowel obstruction (3.6%), and pulmonary embolus (0.41%), while late complications are stomal stenosis (4.73%), bowel obstruction (3.15%), incisional hernia 0.47%, marginal ulcer (0.3–16%) [Podnos et al., 2003; Farrell et al., 2009; Christou et al., 2004; Martin et al., 2011; Azagury DE., 2011; Sacks et al., 2011].

The most common complications associated with LSG include staple line leak (1.17%), post-operative hemorrhage (3.57%), and stenosis of the resected stomach (up to 4%) [Dumon et al., 2011; Parik et al., 2012].

2.6.2. Nutrient deficiencies after bariatric surgery and postoperative replacement prophylaxis

Nutrient deficiencies are common after bariatric surgery. They are related to reduction in food Intake, as well as to the physiological impact of surgically induced anatomical changes in the gastrointestinal tract [Davies et al. 2007]. In a paper of Gehrer et al, the authors point out that prior to bariatric surgery, 57% of the patients had at least one deficiency [Gehrer et al., 2010]. In a review paper, Parrot and colleagues give an overview about the prevelance of (possible) micronutrient deficiencies before weight loss surgery (WLS) and the results are the following: thiamine deficiency as high as 29%; B12 deficiency 2–18%; folate deficiency as high as 54%; iron deficiency as high as 45%; vitamin D deficiency as high as 90%. The same paper describes also the prevalence of micronutrient deficiencies after WLS: B12 deficiency at 2–5years <20% for RYGB and 4–20% for SG; folate deficiency up to 65%; iron deficiency from 3 months to 10 years <18% for SG and 20–55% for RYGB; vitamin D deficiency up to 100% [Parrot et al., 2017]. In a (prospective) study with 99 bariatric patients, Kikkas et al., demonstrated that the risk for cumulative iron and vitamin B12 deficiency 5 years after LSG was 20% and 48%, respectively [Kikkas et al., 2019]. Recent guidelines recommend that all patients pursuing weight loss surgery should undergo a preoperative clinical nutrition evaluation by a registered dietician and all patients after bariatric surgery should use nutritional supplements for life [Mechanick et al., 2020; Parrott et al., 2017].

2.7. Anatomy and physiology of the stomach

2.7.1. Anatomy of the stomach

Topographically, the stomach can be divided into five regions: the cardia and gastroesophageal (GE) junction, the fundus, the corpus, the antrum, and the pylorus. The fundus and the corpus harbor acid-secreting glands, and the antrum harbors the alkaline secreting surface epithelium and the endocrine, gastrin-secreting G-cells [Soybel D., 2005].

2.7.2. Physiology of the stomach

Gastric mucosa

Functionally, the gastric mucosa is divided into acid-secreting and nonacid secreting regions. The acid- and pepsinogen-secreting mucosa is found in the corpus and fundus. The acid secreting unit of the mucosa is the gastric gland. At the base of the gastric gland lie the pepsinogen-secreting chief cells. The middle of the gastric gland is largely populated with the HCl-secreting parietal cells.

Toward the lumen, at the neck, parietal cells are still present, but give way to mucus neck cells and then, near the opening, the mucosa is largely populated with surface epithelial cells. Intercalated between parietal cells and smaller immature cells are enterochromaffin-like (ECL) cells expressing histidine decarboxylase, an enzyme that is essential in the production of the paracrine agonist, histamine [Shubert, 2015; Soybel D., 2005].

Neuroendocrine regulation of acid secretion

Parietal cells are responsible for gastric acid secretion, which aids digestion of food, absorption of minerals and control of harmful bacteria. However, a fine balance of activators and inhibitors of parietal cell-mediated acid secretion is required to ensure proper digestion of food, while preventing damage to the gastric and duodenal mucosa. As a result, parietal cell secretion is highly regulated through numerous mechanisms including the vagus nerve, gastrin, histamine, ghrelin, somatostatin, glucagon-like peptide 1, and other agonists and antagonists. The tight regulation of parietal cells ensures the proper secretion of HCl. The H^+-K^+-ATPase enzyme expressed in parietal cells regulates the exchange of cytoplasmic H^+ for extracellular K^+. The H^+ secreted into the gastric lumen by the H^+-K^+-ATPase combines with luminal Cl^- to form gastric acid, HCl. Inhibition of the H^+-K^+-ATPase is the most efficacious method of preventing harmful gastric acid secretion. Proton pump inhibitors and potassium competitive acid blockers are widely used to therapeutically inhibit acid secretion. Stimulated delivery of the H^+-K^+-ATPase to the parietal cell apical surface requires the fusion of intracellular tubulovesicles with the overlying secretory canaliculus, a process that represents the most prominent example of apical membrane recycling. In addition to their unique ability to secrete gastric acid, parietal cells also play an important role in gastric mucosal homeostasis through the secretion of multiple growth factor molecules. The gastric parietal cell therefore plays multiple roles in gastric secretion and protection, as well as in coordination of physiological repair [Engevik et al., 2019; Ramsay et al., 2011].

Alkaline secretion by the gastric mucosa

The non-acid secreting mucosa of the gastric antrum and pylorus is characterized by the presence of relatively simple glands populated with the mucus- and HCO_3^- – secreting surface epithelium. The surface epithelium, both in the antrum and corpus/fundus regions, is the basis of the ‘‘mucosal barrier’’ [Soybel D., 2005].

Gastric digestion and contributions to downstream absorption

The stomach contributes to digestion of solid food by mixing chyme with acid and pepsin (pepsinogen autoactivated in the presence of luminal acid), which helps break down protein to simple peptides that will be absorbed or broken down further by intestinal peptidases. Subpopulations of parietal cells also secrete intrinsic factor, an essential cofactor in the absorption of vitamin B12 downstream in the terminal ileum. Gastric acid itself enables absorption of

specific metals and nonmetal cations, including Ca^{2+}, Fe^{3+} and other trace metals. At low pH, Ca^{2+} is more fully released from binding bases, and is thus more available for absorption in the duodenum. Similarly, Fe^{2+} auto-oxidizes in the presence of luminal acid, placing it in a form more easily absorbed in the small intestine [Soybel D., 2005].

Gastric motility

The stomach has three layers of muscularis: an inner circular layer, a middle longitudinal layer, and an outer but incomplete oblique layer. Motor functions in the stomach are segregated by the region. The fundus relaxes as fluids and solids enter the esophagus, a response known as receptive relaxation, and further as food actually enters the funds, a process known as adaptive relaxation. This response allows the liquid to pool in the fundic pouch while the solid components of the meal remain in the mainstream of flow toward the pylorus. On the greater curvature, in the muscularis of the upper corpus, lies the primary electrical pacemaker of the stomach. Superimposed on the basic electrical rhythm of the pacemaker, the corpus and antrum engage in a coordinated propulsion of the luminal contents toward the pylorus. The pylorus itself acts as a sieve, remaining open in anticipation of the wave of peristalsis. As the wave advances, small particles pass through the pyloric sphincter; when the wave hits, the pylorus closes, thereby acting as a barricade. The chyme, propelled with increasing velocity against the pyloric sphincter, is thus broken up by enzymatic digestion in combination with mechanical disruption [Soybel D., 2005].

Satiety

The role of the stomach in regulating food intake has become an increasingly important issue, especially with the growing number of procedures for bariatric surgery. In this regard, the recently described hormone ghrelin has assumed central importance. Ghrelin is an appetite stimulating hormone that is released by the gastric mucosa into the portal circulation when the stomach is empty, passing into the central circulation to stimulate appetite centers in the hypothalamus; the circulating levels of ghrelin fall precipitously as soon as the stomach begins to fill. In bariatric surgical procedures with creation of small pouches that distend rapidly, the baseline and premeal peaks of ghrelin are suppressed, suggesting that blunting of ghrelin responses may contribute to suppression of appetite after bariatric surgery. Although ghrelin is by no means the dominating signal for control of satiety, its effects must be understood in the context of other neural and hormonal inputs to satiety centers in the pituitary [Soybel D., 2005].

2.8. Gastric biomarkers

Stomach-specific biomarker testing (“serological biopsy”), being an alternative method to traditional EGDS, can provide a new non-invasive option to evaluate the stomach mucosa and gastric physiology in order to diagnose both functional

disorders and gastric diseases, including HP infection and AG [Agreus et al. 2012; Storskrubb et al. 2008; Syrjänen et al. 2019].

The latest innovation in this technology represents a panel of 4 stomach-specific biomarkers (PgI, PgII, G17 and HPAB) known as GastroPanel® (GP) test (Biohit, Oyj, Finland), which distinguishes between 8 diagnostic biomarker profiles**.** Initially, GastroPanel had 5 diagnostic categories, but the new report includes 3 additional categories **(Figure 5)** [Agreus et al. 2012; Syrjänen et al. 2019].

Pepsinogen I (PgI) is a precursor enzyme of pepsin**,** synthesized by the chief cells and the neck cells of the gastric corpus. As a pepsin precursor, the major part of PgI is excreted into the gastric lumen, but a minor fraction is released into the blood circulation. Concentration of circulating PgI is strongly correlated with quantity of chief cells in the corpus, and any loss of these cells due to mucosal atrophy results in a linear decrease in blood PgI levels [Syrjänen et al., 2019].

Pepsinogen II (PgII) is produced by the chief cells and the mucous neck cells of the gastric corpus, in the pyloric glands of the antrum, as well as in Brunner's glands of the proximal duodenum. Elevated PgII level as a stand-alone marker reflects mucosal inflammation, the highest values usually being detected in HP-associated active gastritis [Syrjänen et al., 2019].

Gastrin-17 (G17). Gastrins are linear peptide hormones produced by the G-cells in the duodenum, in the pyloric part of the antrum, and in the pancreas. The main function of gastrins is to stimulate the secretion of gastric acid by the parietal cells in the corpus, as well as to increase the motility of the antrum. In addition, gastrins are known to stimulate gastric chief cells to secrete PGs, and also to induce the contraction of the lower esophageal sphincter. The dominating forms of gastrin in plasma/serum are amidated G-34 and amidated G-17, the latter, however, being specifically of antral G-cell origin. In the healthy antrum, G-17 is the most potent form of all gastrins. Plasma G-17 levels within the normal range indicate a normal structure and function of the antrum, whereas low or high values of G-17 reflect abnormalities in acid output by the corpus**.** Gastrin-17 concentration in blood during fasting (G17 basal (G17b)) falls as the acidity of the gastric contents rises (pH below 2.5) (less than 1 pmol/l indicates an increased secretion of hydrochloric acid). The gastrin-17 (basal) value also falls in the case of antrum mucosa atrophy, where G-cells disappear. Low gastrin-17 levels in blood during fasting may therefore indicate either an increased secretion of hydrochloric acid or antrum mucosal atrophy. Antrum mucosa atrophy, however, is dependent upon infection with HP. If gastrin-17 concentration is above 7 pmol/l, it is usually due to decreased secretion of hydrochloric acid. Distinguishing between antrum mucosa atrophy caused by HP infection and an increased secretion of hydrochloric acid (gastrin17 basal <1 pmol/l) can be performed by measuring the response of

gastrin-17 after protein stimulation (G17 stimulated (G17s)). If a person has been infected by HP and his/her gastrin-17 value is still low after protein stimulation (less than 3 pmol/l), it may indicate atrophic gastritis of the antrum. However, if HP antibody levels are not elevated, the results indicate increased secretion of hydrochloric acid [Syrjänen et al., 2019]. Gastrin-acid feedback mechanism is shown in **Figure 6**.

Helicobacter pylori antibody (HPAB). HP infection is the most important cause of chronic gastritis resulting in atrophic gastritis (AG) over time. In the stomach, HP is found within the mucous layer overlying the gastric epithelium, and within the mucosal glands, but it does not appear to invade the epithelial cells. The mucosa underneath and surrounding the areas of HP colonization is invariably inflamed. This condition is referred to as chronic superficial or non-atrophic gastritis [Syrjänen et al., 2019].

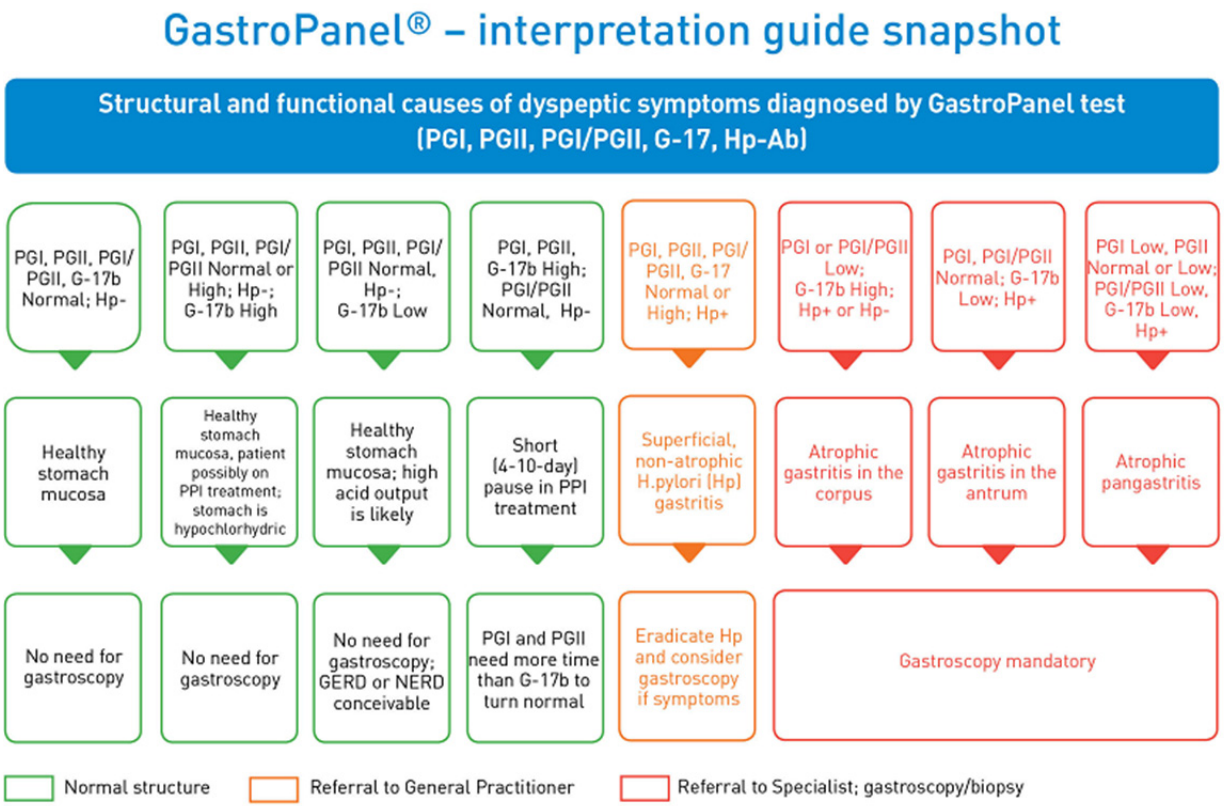
2.9. Interpretation of the biomarker profile

The manufacturer-validated reference values of the four biomarkers are the following: PgI 30–160µg/l; PgII 3–15µg/l; PgI/PgII ratio 3–20, G17b 1–7pmol/l; G17s 3–30 pmol/l; HPAb<30EIU [Storskrubb et al. 2008].

Based on the blood plasma levels of these biomarkers after fasting or after food (protein rich drink) stimulation, a GastroPanel® report is obtained from which valuable conclusions can be drawn about the structure and function of the gastric antral and corpus (oxyntic) mucosa, as well as about acid secretion or stomach acidity [Agreus et al. 2012].

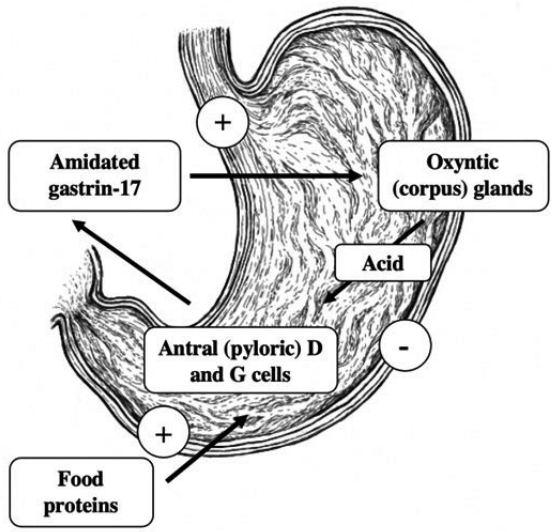
The results are interpreted, using the special GastroSoft® software, by classifying them according to the biomarker levels, under one of the eight diagnostic categories (**Figure 5**):

1) normal profile
2) superficial (HP) gastritis – (PgI, PgII, PgI/PgII, G-17 normal or high; HPAb >30EIU)
3) atrophic gastritis of the antrum (AGA) – (PgI, PgI/PgII normal; G-17b low; HPAb>30EIU) 4) atrophic gastritis of the corpus (AGC) – (PgI, PgI/PgII low; G-17b high; HPAb <30EIU or >30EIU)
5) atrophic pan-gastritis (AG of the antrum and corpus) – (AGP) (PgI low, PgII normal or low; PgI/PgII low, G-17b low; HPAb >30EIU),
6) normal (healthy) stomach, high acid output – PgI, PgII, PgI/PgII, G17(s) normal; G17(b) low; HP-negative
7) normal (healthy) stomach, low acid output – PgI, PgII normal or high; PgI/PgII normal; G17 (b) high; HP-negative: eg. patients receiving PPI treatment
8) mucosal „state“ caused by a pause after continuous PPI treatment – PgI, PgII, G17(b) high; PgI/PgII norm; HP-negative. It is usually followed by „Rebound acid hypersecretion“ (G17b levels extremely low) [Agreus et al. 2012; Sipponen et al., 2007; Syrjänen et al., 2019].



PGI – Pepsinogen I; PGII – Pepsinogen II; G-17b – basal (fasting) Gastrin 17; GERD – gastroesophageal reflux disease; NERD – Non-erosive reflux disease; PPI – proton pump inhibitor

Figure 5. Interpretation of GastroPanel biomarker test [Biohit Oyj., 2023]



+ – positive feedback; − – negative feedback

Figure 6. Mechanism of gastrin-acid feedback control (Figure by T. Veršinina)

3. SUMMARY OF THE LITERATURE REVIEW

Obesity, defined as abnormal or excessive fat accumulation, is a major health issue affecting about 650 million of the world`s adult population. Obesity has been declared a chronic prog- ressive disease that substantially increases the risk of diseases such as T2DM, fatty liver disease, hypertension, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnoea. Obesity carries a major economic burden.

Obesity is the result of the interplay between heterogenic factors, deriving from a person's eating behaviour, physical activity and individual energy expenditure determinants. Multiple options have been described for treating overweight and obesity. However, since lifestyle interventions and medical therapy have limited effectiveness in reducing weight, then bariatric surgery has gained popularity, as it is the the only effective way to treat obesity in the long term. Nowadays, a variety of surgical options are currently offered for treatment of obesity, RYGB and SG being the two most common bariatric procedures performed in the world. The mechanisms of bariatric operations contributing to weight loss can vary in the different type procedures, being often combined. These mechanisms include effects on regulation of energy balance, both the central and peripheral nervous systems` regulation of appetite and metabolism, but also changes in gut hormones and microbioma.

As most bariatric procedures show similarly good results in excess weight loss, then multiple aspects (GERD, hiatal hernia, nutrient deficiencies) have to be considered when choosing the operation type. Bariatric surgery procedures are safe and carry a low risk of complications, especially when performed by experienced bariatric surgeons, in the setting of specialized centers.

Stomach-specific biomarker testing ("serological biopsy"), being an alternative method to traditional EGDS, can provide a new non-invasive option to evaluate the stomach mucosa and gastric physiology in order to diagnose both functional disorders and gastric diseases, including HP infection and AG. The latest innovation in this technology represents a panel of 4 stomach-specific biomarkers (PgI, PgII, G-17 and HPAB) known as GastroPanel® test, which distinguishes between 8 diagnostic biomarker profiles**.** Based on the profiles, a report is obtained from which valuable conclusions can be drawn about the structure and function of the gastric antral and corpus (oxyntic) mucosa, as well as about acid secretion or stomach acidity.

4. AIMS OF THE STUDY

1) To find out if less invasive serological biomarker testing could avoid invasive preoperative endoscopies in obese patients referred to bariatric surgery.
2) To study the function of the gastric mucosa and acid secretion after bariatric surgery: changes in the gastric biomarker profile up to 2-year follow-up after bariatric surgery.
3) To evaluate whether postoperative gastric biomarker changes are related to operation and anatomical changes alone, or whether there could occur also some patohistological alterations of the gastric mucosa; also how soon changes in biomarker levels develop postoperatively.
4) To evaluate whether preoperative, postoperative or preoperative/postoperative rate of stomach-specific biomarkers is correlated with excess weight loss at 1-year follow-up and whether a relevant test could be used as an additional tool to select the most appropriate operation type (LSG, LRYGB) for each bariatric patient.

5. MATERIAL AND METHODS

5.1. Patients

The whole study is based on the data of 105 patients (33 male, 72 female) who underwent bariatric operation at the Surgery Clinic of Tartu University Hospital between 2008 and 2016 **(Table 1)**. Some patients were involved in several studies. Approval was obtained from the Research Ethics Committee of the University of Tartu, license no. 218/T-6.

Table 1. Characteristics of publications

Study type and period of data collection	No of patients (male/female)	Goals of the study	Journal (No)
Prospective 2008–2011	40 12/28	Gastric biomarker profile after bariatric surgery	Hepatogastroenterology (I)
Prospective 2013–2015	65 21/44	Preoperative correlation of gastric biomarkers with gastrobiopsies	BMC Obesity (II)
Prospective 2013–2016	57 16/41	Dynamics of gastric biomarkers during 1-year follow-up after bariatric surgery	Surgery, Gastroenterolo- gy and Oncology (III)

5.2. Inclusion and exclusion criteria

The eligible patients were adults aged 18 years and older with a BMI of >40 or >35, with certain obesity-related comorbidities (hypertension, diabetes, dyslipidaemia, sleep apnea, osteoarthritis, polycystic ovarian syndrome), providing informed written consent for participation in the study. Patients who were younger than 18 years or did not meet the criteria for bariatric operation or who were unwilling to participate in the study were excluded.

Patients who participated in the study were interviewed, tested by GP, and subjected to esophagogastroduodenoscopy examination with directed biopsies.

5.3. Patient questionnaire

In all patients, eligible for bariatric operation and willing to participate in the study, medical history (co-morbidities, medications, prior operations, allergy) and physical parameters (height, weight, BMI, waist circumference) were recorded. Also the patients were interviewed using a standardized questionnaire about the specific history of upper abdominal complaints (heartburn, reflux,

dyspepsia). The interview was conducted prior to biomarker test, EGDS and surgery (Publication II), during the follow-up visit at 1, 3, 12 months (Publication III) and 2 years (Publication I) after bariatric surgery.

5.4. Biomarker test examination

Blood samples were collected for GP testing preoperatively and were repeated at postoperative days 1 and 3, and subsequently at 1-, 3, 12 months and 2 years postoperatively (in different study groups). GP biomarker test was conducted according to the Biohit standard rules: the patient had to be starved for at least 10 hours before the study (no food, no liquids), smoking was prohibited 4–10 hours before the study. The patient was not allowed to use antacides, PPI-s and histamine blockers for at least 1 week.

Blood was collected and processed according to the instructions given by the manufacturer of GP biomarker test (GastroPanel; Biohit, Plc, Helsinki, Finland): 10 mL of fasting blood were collected, plasma was separated, a specific gastrin stabilizer (Biohit Plc, Helsinki, Finland) was added, and the sample was stored at -70ºC until analysis. After drawing the basal (fasting) sample, the patient drank a protein rich drink; after 20 minutes a second blood sample (stimulation sample) was collected (10 mL) and the above described procedure for sample preservation was carried out. All samples were properly stored and transported to the service laboratory of Biohit Oyj for analysis. The plasma levels of the following biomarkers were measured with the ELISA assay: fasting (basal) PgI and PgII, G17b and G17s and HPAB. All assays were carried out in duplicate at the service laboratory of Biohit Plc (Helsinki, Finland) [Syrjänen et al., 2019; Sillakivi et al., 2013].

5.5. Interpretation of GastroPanel

GP is an automated ELISA test that measures the plasma levels of the following biomarkers: PgI and PgII, G17b and G17s, HPAB. The manufacturer-validated reference values of the four biomarkers were used: PgI 30–160µg/l; PgII 3–15µg/l; PgI/PgII ratio 3–20, G17b 1–7pmol/l; G17s 3–30 pmol/l; HPAB<30EIU [Storskrubb et al. 2008; Dixon et al., 1996].

The results are interpreted, using the special GastroSoft® software, by classifying the results, according to the biomarker levels, under one of the five diagnostic categories:

1) normal profile
2) superficial (HP) gastritis – (PgI, PgII, PgI/PgII, G-17 Normal or High; HPAB >30EIU)
3) atrophic gastritis of the antrum (AGA) – (PgI, PgI/PgII Normal; G-17b Low; HPAB>30EIU)
4) atrophic gastritis of the corpus (AGC) – (PgI, PgI/PgII Low; G-17b High; HPAB <30EIU or >30EIU)

5) atrophic pan-gastritis (AG of the antrum and corpus) (AGP) – (PgI Low, PgII Normal or Low; PgI/PgII Low, G-17b Low; HPAB >30EIU), as detailed elsewhere [Agreus et al., 2012; Sipponen et al., 2007].

At the time we conducted our study, GP had 5 different marker profiles, while the new (updated) version includes 8 profiles [Syrjänen et al., 2019].

5.6. Esophagogastroduodenoscopy

Routine EGDS examination with directed biopsies was performed preoperatively (Publications II and III) and 12 months after bariatric operation (in SG patients) (Publication III)

All endoscopic evaluations were carried out using pharyngeal anesthesia with 4% Lidocaine gel on the scope. Biopsy speciemens were obtained using standard biopsy forceps.

During EGDS, the esophageal, gastric and duodenal mucosa was visually inspected and abnormalities were detected. The degree of esophagitis was evaluated according to the Los Angeles classification (LA) [Armstrong et al. 1996]. In every patient, two biopsies from the antrum (2cm from the pyloric ring) and two biopsies from the corpus were collected. Additional biopsies were taken only when necessary.

All endoscopies were performed at the Surgery Clinic of Tartu University Hospital, Department of Abdominal Surgery by, two endoscopists (JS, TS).

5.7. Histology and H. pylori

The histology of the biopsies was evaluated separately for the gastric antrum and corpus, according to the updated Sidney System (USS) classification [Dixon et al. 1996], by 3 independent pathologists (ZR, KS, PS). In the case of discrepant results, the biopsies were re-evaluated by a pathologists` panel, and the consensus diagnosis was used as the final one. The biopsy specimens were fixed overnight in neutral buffered formalin and stained for morphological and HP examinations using the hematoxylin-eosin method and the Giemsa method. At histopathological evaluation, chronic gastritis, inflammation activity, mucosal atrophy and intestinal metaplasia were classified as follows**:** none, mild, moderate, severe. HP-colonization and its abundance were semi-quantitatively estimated, separately in the antral and corpus mucosa, by microscopic counting, as absent, mild, moderate and severe, as described earlier [Stolte et al. 1989; Peetsalu et al., 2005].

5.8. Surgical procedures

Laparoscopic Sleeve Gastrectomy and Laparoscopic Roux-en-Y gastric bypass operations (according to the standardised laparoscopic technique) were used for the study patients **(Figure 4)**.

The SG provides reduction in the gastric volume through vertical stapler resection along the greater gastric curvature. A major part of the corpus and a small part of the antrum were resected, leaving a remnant (tubular gastric „sleeve“) of 10–15% of the initial stomach comprising a certain amount of both the antral and corpus mucosa. In the case of SG, a bougie size of 35 Fr was used and resection of the stomach was started at 4 cm from the pylorus, the volume of the created sleeve was about 100–120ml. The weight of the resected stomach was measured using an electronic scale and the volume of the resected stomach was measured using a tap water test (a small hole was made in the corner of the specimen and was filled with tap water until the water poured out of the created defect) as described earlier [Weiner et al., 2007].

RYGB is a combined gold standard method where, by horizontal division separating the upper part of the stomach with the use of staplers, a new, smaller stomach is formed, while more than 90% of it is bypassed and excluded from the food passage. In RYGB, the volume of the created pouch is about 30–50 ml, the length of the biliopancreatic limb is 50–60 cm and the length of the alimentary limb is 120 cm. Food is directed from this small pouch into the middle part of the small intestine through a gastro-jejunal anastomosis. No organs are removed, nor are any resections carried out.

5.9. Statistics

The data were analysed using Statistica® version 10.0 and the 13 software package. Continuous variables were presented as mean (M) values with standard deviation (SD), and nominal variables were presented as relative fequencies. Comparison between the groups was performed using the two-sample *t*-test or the Mann-Whitney *U* test for continouous variables, where appropriate, and Fisher's exact test for nominal variables. All statistical tests were two-sided and $p \leq 0.05$ was considered significant.

5.10. Study groups

Publication II

In a prospective study, conducted between January 2013 and September 2015, 65 patients referred to bariatric surgery at the Surgery Clinic of Tartu University Hospital, were included and data was collected according to a standardised protocol (Methods).

According to the Gastropanel results, all patients were divided into 2 groups: HS (Healthy stomach) group and NHS (Non-healthy stomach) group. In the HS stomach group all biomarkers were normal. In the NHS group one or more biomarker levels were abnormal, describing the following pathological conditions: 1) Non-atrophic H. Pylori (HP+) gastritis – only H. Pylori antibody test was positive; 2) atrophic antrum gastritis – PgI, PgI/PgII normal; G17(b) low; HP+; 3) atrophic corpus gastritis – PgI and/or PgI/PgII low; G17(b) high; HP+ or HP-; 4) atrophic pangastritis (antrum and corpus) – PgI low, PgII normal or

low; PgI/PgII low; G17(b) low; HP+. Gastropanel test results in the HS group and the NHS group were evaluated against the gold standard, EGDS with biopsies.

The aim of the study was to find out if the data collected from endoscopic findings and gastrobiopsies correlates with the results of GP. Another aim was to ascertain if GP test as a less invasive method can be used instead of EGDS in selected patients undergoing elective bariatric surgery.

Publication III

This prospective study of 57 bariatric patients is a continuation of a study conducted between 2013 and 2015 at Tartu University Hospital. Altogether 29 LSG and 28 LRYGB patients, matched according to preoperative BMI, sex and age, were included in the study population. The data was collected according to a standardised protocol pre- and postoperatively (Methods). The study describes changes in the biomarker profile in different operation groups (LRYGB and LSG) during 1- year follow-up after bariatric surgery and compares the biomarker profile with the data of histopathological evaluation of the samples collected on EGDS preoperatively and 12 months postoperatively (only the LSG group).

The main aim of the study was to evaluate whether postoperative changes in gastric biomarkers are related to operation and anatomical changes alone, or whether there could occur also some patohistological alterations of the gastric mucosa; also how soon the changes in biomarker levels develop postoperatively. Another aim was to to evaluate whether preoperative, postoperative or preoperative/postoperative rate of stomach-specific biomarkers is correlated with excess weight loss at 1-year follow-up.

Publication I

Publication I is based on the investigastion of the biomarker profile of 40 patients 2 years (average 22 months) after bariatric surgery (LSG and LRYGB operations). There were 12 male and 28 female patients in the study group who had undergone either SG or RYGB operation. Twenty SG and 20 RYGB patients, previously matched according to preoperative BMI, postoperative time, sex and age, were selected and included in the study.

All patients were interviewed using a standardised questionnaire and blood samples were collected for biomarker testing (Methods).

The aim of the study was to compare the stomach specific biomarker profile between the SG and RYGB groups.

6. RESULTS

6.1. Correlation between gastric biomarkers and gastrobiopsies (Publication II)

The key characteristics of the study patients are presented in **Table 2**.

Table 2. Key characteristics of the patients (Publication II)

Patient characteristics	
Mean age, years (SD)	43.1 (9.08)
Female patients, n (%)	44 (67.7)
Mean preoperative weight, kg (SD)	128.3 (21.5)
Mean preoperative body mass index, kg/m² (SD)	44.3 (5.12)
Concomitant diseases, n (%)	57/65 (87.7)
Type II diabetes, n (%)	9 (13.8)
Hypertension, other cardiac diseases, n (%)	39 (60)
Obstructive sleep apnea, n (%)	20 (30.7)
Degenerative joint disease, n (%)	13 (20)
Hypercholesterolemia, n (%)	42 (64.6)
Smokers, n (%)	17 (26.1)

SD – standard deviation

According to the Gastropanel test results, 22 (34%) patients were classified into the HS group and 43 (66%) into the NHS group. There was a statistically significant difference in the mean PgI, PgII, PgI/PgII and IgG values between the HS and NHS groups ($p<0.001$) **(Table 3)**.

Table 3. Biomarker levels for the two categories (HS/NHS) of patients (Publication II)

Biomarkers	**Whole Series**	**HS Group n=22**	**NHS Group n=43**	**p-value***
Mean G17b± SD, pmol/l (ranges)*	3.9±5.0 (0–28.1)	2.05±2.2 (0–9.9)	4.9±5.7 (0–28.1)	**0.028**
Mean G17s± SD, pmol/l (ranges)**	12.3±10.3 (0–40.9)	8.8±8.4 (0.2–36.1)	14.1±10.8 (0–40.9)	**0.048**
Mean PG I± SD, µg/I (ranges)	81.8±38.6 (22.7–197.5)	58.2±27.9 (33.0–151.1)	93.9±38.0 (22.7–197.5)	**<0.0001**
Mean PG II± SD, µg/I (ranges)	7.2±5.9 (0.3–29.3)	3.37±1.7 (0.3–8.4)	9.2±6.4 (1.4–29.3)	**<0.0001**
Mean PG I/PG II±SD, µg/I (ranges)	15.5±12.3 (3.3–103.3)	21.6±18.9 (10.7–103.3)	12.4±4.6 (3.2–25.2)	**<0.0001**
Mean IgG±SD, EIU (ranges)	64.2±40.8 (2.1–121.1)	13.12±7.7 (2.1–27.3)	90.4±21.1 (38.1–121.1)	**<0.0001**

HS – Healthy stomach; NHS – Non-healthy stomach; G17b – basal gastrin-17; G17s – stimulated gastrin-17; *Mann-Whitney U-Test

The concordance between GastroPanel test and USS histology (5 categories in both) is shown in **Table 4**. Agreement between the two methods was significant: Kappa=0.68 (95% CI 0.504–0.854), with an overall agreement of 55/65 (84.6%; 95% CI 73.9–91.4%) across the five diagnostic categories.

The prevalence of HP infection in the entire cohort was 43/65 (66%) in GP test and 41 (63%) in the histological evaluation of the biopsies. In the HS group 6/22 (27%) of patients had mild chronic HP-negative gastritis of the antrum and corpus without a significant difference in their biomarker level compared with the other patients in that group.

In the NHS group, of all patients with histologically confirmed chronic gastritis, 4 had moderate degree AGA. The biomarker test also confirmed those 2 AGA cases (G17b and G17s were low in the first case and G17s response was below a threshold of 3 pmol). One patient, who was classified as a case of panatrophy by GastroPanel, had moderate degree chronic gastritis of the antrum and corpus with mild degree HP infection, but no atrophy.

Four patients in the HS group and 10 in the NHS group had endoscopically confirmed esophagitis, while 2 and 8 of them respectively, had also reflux complaints **(Table 5)**.

According to the results of our study, preoperative EGDS could have been avoided in 31% of the patients (20/65) in the study group.

We did not find any correlelation between G17b and esophagitis at EGDS, or between G17b levels and GERD complaints.

Table 4. Concordance between biomarker test results and histological diagnosis (Publication II)

Diagnostic categories of the GastroPanel test	**Gastric mucosa histology (USS classification*)**					
	Normal	Superficial (HP) Gastritis	Antral atrophy (AGA)	Corpus atrophy (AGC)	Panatrophy (AGP)	**Total**
Normal profile	16	6	0	0	0	**22**
Superficial (HP) Gastritis	0	38	3	0	0	**41**
Antral atrophy	0	0	1	0	0	**1**
Corpus atrophy	0	0	0	0	0	**0**
Panatrophy	0	1	0	0	0	**1**
Total	**16**	**45**	**4**	**0**	**0**	**65**

*The Updated Sydney System (USS) classification of gastritis

Table 5. Endoscopic findings and clinical symptoms in pre-operative assessment of the HS and NHS groups (Publication II)

Endoscopic findings	Healthy stomach (HS Group) n=22	Non-healthy stomach (NHS Group) n=43
Hiatal hernia	4	15
Esophagitis	4	10
Erosions/erosive gastritis	3	14
Duodenal polyp	-	1
GERD*	2	8

GERD – gastroesophageal reflux disease; *clinical symptom

6.2. Changes in the biomarker profile in different operation groups (LRYGB and LSG) during 2- year follow-up after bariatric surgery (Publications III, I)

The key clinical characteristics of the study groups are presented in **Table 6** (Publication III) and **Table 7** (Publication I).

Tables 8 and 9 show the gastric biomarker levels (in dynamics) of LSG and LRYGB patients from 2 different studies (Publications III and I).

In the LSG group PgI level declined rapidly after surgery and at 12 months follow-up mean PgI level was significantly lower (20.5 μg/L), compared to its preoperative level (75 μg/L), ($p<0.0001$) (Publication III). Data from Publication I showed that 2 years after surgery, PgI values were almost identical to those described at 1-year follow-up (Publication I). Abnormally low PgI level (<30 μg/L) in the LSG group was seen in 82% of the cases at 12-month follow-up (Publication III) and in 80% of cases 2 years after surgery (Publication I). PgI values in the LRYGB group increased from 1POP day to 3POP day and started to decrease at 1-month follow-up, being significantly lower (32.3 μg/L) at 12-month follow-up compared to their preoperative values ($p<0.0001$) (**Table 9**, Publication III). Two years after LRYGB operation, the mean value of PgI in the study group was 32.2 μg/L (**Table 9**, Publication I). PgII level and the PgI/PgII ratio declined after surgery, being significantly lower at 12 months compared to their preoperative values (PgII $p<0.0006$; PgI/PgII $p<0.0001$) (**Table 9**, Publication III)**.** Low levels of PgII and a low PgI/PgII ratio was seen 2 years after surgery in the LSG group (**Table 8**, Publication I).

In the LRYGB groups, PgI and PgII levels rose markedly during the first 3 postoperative days, thereafter their levels and the PgI/PgII ratio declined significantly (**Table 9**, Publication III).

Table 8 presents a 83% increase in the mean G17f values to 7.9pmol/L in the LSG group by the end of one POP year (Publication III). The results from Publication I showed that in the LSG group mean G17f level was high 2 years after surgery (13.9 pmol/L), and the proportion of cases with G17f exceeding the upper normal cut-off limit was 40% (**Table 8**, Publication I). In the LRYGB

group, the mean values of G17f increased slightly immediately after operation and declined to relatively low levels, i.e., 2.5pmol/L at year 1 (**Table 9**, Publication III). Two years after LRYGB operation, the mean values of G17f in the study group was 3.1pmol/L (**Table 9**, Publication I).

In the LSG groups, G17s was normal (response >3 pmol/l) in 40% of the cases at year 1 (**Table 8**, Publication III) and in 100% of the cases at 2 years after the operation (**Table 8**, Publication I).

In the LRYGB groups, 7.4% of the cases showed a normal stimulation response of G17 at one-year follow-up and 25% of the cases 2 years after the operation (**Table 9**, Publication III and Publication I).

Preoperative histopathological findings confirmed chronic gastritis in 79.3% of the LSG patients and in 67.9% of the LRYGP patients (**Table 10**, Publication III). The prevalence of HP colonization was high in both groups, at 62.1% and 61%, respectively. Postoperative histopathological findings revealed no substantial changes in chronic gastritis scores for LSG patients (in one case moderate degree antral mucosa atrophy had resolved). HP colonization reduced from 62% to 44% (**Table 10**, Publication III).

According to the Spearman test, the preoperative- and one-year follow-up levels of the gastric biomarkers (PgI, PgII G17f and G17s, HPAB) and the preoperative/one-year ratio did not correlate with %EWL at 1 year either in the LSG or the LRYGB group (all p=NS).

Table 6. Key characteristics of the LSG and LRYGP patients (Publication III)

	LSG group n=29	LRYGP group n=28	p-value
Preoperatively			
Mean age, years (SD)	42±10.7	43±7.9	0.776
Females	21	20	0.999
Mean weight, kg (SD)	127±24.0	128±18.4	0.909
Mean body mass index, kg/m² (SD)	44±5.6	44±4.9	0.959
Mean weight of removed gastric specimen, g (SD)	159.1±37.1	-	
Mean volume of removed gastric specimen, ml (SD)	692.2±167.2	-	
Postoperatively (1-year follow-up)			
Mean weight, kg (SD)	86.8±21.8	92.7±15.9	0.253
Mean body mass index, kg/m² (SD)	30.0±5.7	31.6±4.6	0.238
Mean excess weight loss % (SD)	77.3±25.4	65.1±21.3	0.054

LSG – laparoscopic sleeve gastrectomy; *LRYGP* – laparoscopic Roux-en-Y gastric bypass; *SD* – standard deviation

Table 7. Demographic data of the LRYGB and LSG patient groups (Publication I)

Time period	Patient data	**LRYGB n=20**	**LSG n=20**	**p-value**
Preoperative	Male/female ratio	6/14	6/14	NS
	Mean age, years	44.1	47.2	NS
	Mean BMI, kg/m²	49.0	47.8	NS
Postoperative	Follow-up (months from operation)	21.6	22.7	NS
	Mean BMI, kg/m²	33.45	32.2	NS
	Mean excess weight loss %	62.9	67.2	NS

LSG – laparoscopic sleeve gastrectomy; *LRYGP* – laparoscopic Roux-en-Y gastric bypass

Table 8. Gastric biomarkers (in dynamics) for the LSG patients (Publications III and I)

Publication III									**Publication I**
Biomarkers	**Preoperative**	**1 day POP**	**3 day POP**	**1 month POP**	**3 months POP**	**12 months POP**	**Change of mean values, 1 year vs preoperative (%)**	**P value (mean preoperative vs 1year POP)**	**22 months POP**
Mean PG I±SD (range) µg/L	75±30.1 (34.4–154.6)	32.1±21.6 (5.3–109.9)	16.6±11.3 (2.8–47.6)	13.2±7.5 (2–39.4)	18.3±13.9 (0.8–53.3)	20.5±9.6 (7.9–46.6)	-73%	<0.0001	20.0 ±11.5 (4.3–43.8)
PG I is abnormally low (<30 µg/L) (percentage)	0%	54%	82%	96%	82%	82%		<0.0001	80%
Mean PG II±SD (range) µg/L	6.1±4.1 (1.1–16)	3.8±2.5 (1.1–12.9)	1.5±1.0 (0–3.9)	2.1±1.5 (0.4–6.8)	2.9±2.4 (0.6–10.7)	4.3±2.9 (1.3–12.8)	-30%	0.0006	4.3 ±1.8 (1.9–8.2)
PG II is abnormally low (<3 µg/L) (percentage)	10%	46%	89%	79%	64%	39%			30%
Mean PGI/PGII±SD (range)	14.7±5.6 (3.2–31.1)	8.9 ±3.6 (2.1–17)	13.2 ±9.6 (3.2–51.5)	8.1 ±5.5 (2.5–28.2)	7.3 ±3.7 (1.3–16.1)	5.5 ±2.3 (1.7–11.8)	-63%	<0.0001	4.8 ±2.3 (1.6–9.9)
PGI/PGII is abnormally low (<3) (percentage)		3.6%	0%	10.7%	3.6%	7.1%			25%
Mean G17f±SD (range) pmol/L	4.3±6.4 (0.1–28.1)	11.8±9.5	10.1±11.8 (0.01–42.3)	6.5±7.5 (0.01–26.3)	7.5±9.1 (0–42)	7.9±11.2 (0.1–46.5)	+83%	0.0356	13.9 ±17.2 (2–58.7)
G17f is abnormally high (>7pmol/L) (percentage)	13.8%	60.7%	42.9%	32.1%	35.7%	32%			40%
Mean G17s±SD (range) pmol/L	9.9±9.1 (0–40)		13.2±12.0 (0.3–49.9)	13.1±9.1 (0–41.3)	12.7±8.2 (0–30.6)	14.6±12.8 (0.1–45.8)	+48%	0.0109	21.3 ±16.6 (3.8 –60.8)
Stimulation response of G17 normal (>3 pmol/L) (percentage)	58.6%		14.3%	39.3%	33.3	40%			100%
Helicobacter pylori positive (percentage)	65.5%					53.6%		0.364	45%

LSG – laparoscopic sleeve gastrectomy; *POP* – postoperatively; *PG I* – Pepsinogen I; *SD* – standard deviation; *PG II* – Pepsinogen II; *G17f* – fasting (basal) Gastrin 17; *G17s* – stimulated amidated Gastrin 17

Table 9. Gastric biomarkers (in dynamics) for the LRYGP patients (Publications III and I)

Publication III									**Publication I**
Biomarkers	**Preoperative**	**1 day POP**	**3 day POP**	**1 month POP**	**3 months POP**	**12 months POP**	**Change of mean values, 1 year vs preoperative (%)**	**P value (mean preoperative vs 1year POP)**	**22 months POP**
Mean PG I±SD (range) µg/L	84.3±44.0 (22.7–186.8)	169.8±68.4 (71.2–356.4)	200.5±61.7 (70.7–400)	33.2±21.5 (1.8–91.6)	33.9±25.6 (10.8–125.3)	32.3±20.4 (11–88)	-62%	<0.0001	32.2 ±12.2 (13.5–55.0)
PG I is abnormally low (<30 µg/L) (percentage)	3.6%	0%	0%	58.3%	65.2%	59.3%			40%
Mean PG II±SD (range) µg/L	7.9±6.9 (0.3–29.3)	17.3±11.7 (3–50)	29.7±22.4 (1.7–73.3)	3.5±3.3 (0.4–16.2)	4.4±4.2 (1.1–20.6)	6.8±5.2 (1.1–20.9)	-14%	0.5219	5.5 ±2.3 (1.6–11.2)
PG II is abnormally low (<3 µg/L) (percentage)	25%	0%	8%	66.7%	60.9%	18.5%			10%
Mean PGI/PGII±SD (range)	16.9±17.7 (3.9–103.4)	12.8±6.6 (4–34)	12.5±12.1 (2.7–61.8)	12.7±9.8 (0.5–49.7)	9.9±5.4 (2.6–22.7)	5.0±3.5 (1.4–13.8)	-70%		6.6 ±2.9 (1.7–11.7)
PGI/PGII is abnormally low (<3) (percentage)	0%	0%	12%	4.2%	4.4%	18.5%		0.0016	10%
Mean G17f±SD (range) pmol/L	3.55±3.38 (0–12.6)	4.11±4.83 (0–23.5)	4.49±5.48 (0–19.8)	4.19±9.66 (0–46.6)	2.68±3.60 (0–11.1)	2.56±3.67 (0–12.3)	-28%	0.294	3.1 ±4.3 (0–15.0)
G17f is abnormally high (>7pmol/L) (percentage)	14.3%	24%	20%	12.5%	17.4%	11.1%			15%
Mean G17s±SD (range) pmol/L	14.4±10.9 (1.5–40)		4.7±5.6 (0.2–19.2)	5.1±11.5 (0–54.3)	2.4±3.7 (0–14.2)	2.9±4.6 (0–20.7)	-80%	<0.0001	2.6 ±3.8 (0–14.2)
Stimulation response of G17 normal (>3 pmol/L) (percentage)	75%		16.7%	0%	0%	7.4%			25%
Helicobacter pylori positive (percentage)	64.3%					48.2%		0.233	50%

LRYGP – laparoscopic Roux-en-Y gastric bypass; *POP* – postoperatively; *PG I* – Pepsinogen I; *SD* – standard deviation; *PG II* – Pepsinogen II; *G17f* – fasting (basal) Gastrin 17; *G17s* – stimulated amidated Gastrin 17

Table 10. Stomach histology of the LSG and LRYGP patients (Publication III)

Histological findings	**Preoperatively LSG n=29**	**Postoperatively LSG* n=25**	**Preoperatively LRYGP** n=28**
Normal, n (%)	6 (20.7)	2 (8)	9 (32.1)
Chronic gastritis	23 (79.3)	23 (92.0)	19 (67.9)
- with moderate or severe corpus atrophy	0 (0)	0 (0)	0 (0)
- with moderate or severe antrum atrophy	1 (4.3)	0 (0)	3 (15.8)
Helicobacter pylori positivity	18 (62.1)	11 (44)	17 (60.7)

* postoperatively 4 patients in the LSG group refused to undergo EGDS; ** in LRYGP group, postoperative EGDS was not performed; *LSG* – laparoscopic sleeve gastrectomy; *LRYGP* – laparoscopic Roux-en-Y gastric bypass; *EGDS* – esophagogastroduodenoscopy

7. DISCUSSION

The knowledge of alterations in stomach physiology after bariatric surgery is an important clinical issue. The sequelae caused by resections or bypasses are persistent and will remain and act over many postoperative years or even decades. Since the number of bariatric operations is growing worldwide, the possibility to evaluate the "health" of the gastric mucosa pre- and postoperatively, using noninvasive methods, would be very attractive, especially in patients after (mini) gastric bypass operation when evalution of the gastric remnant with routine gastroendoscopy is impossible.

The present study is the first where the utility of biomarker test in the preoperative management of bariatric surgery patients was evaluated in a 100% biopsy-confirmed clinical setting.

Using gastroscopic biopsies as the gold standard, the concordance between biomarker testing and histology was substantial, with a kappa value of 0.68 and an overall agreement (across 5 categories) of 84.6%. These values favorably compete with those reported in previous validation studies [Agreus et al., 2012; Storskrubb et al., 2008]. This is not unexpected because the biomarker test used (GastroPanel) is based on four biomarkers reflecting the function and structural integrity of the stomach mucosa [Agreus et al., 2012; Sillakivi et al., 2013; Storskrubb et al., 2008; Sipponen et al., 2007; Telerenta-Keerie et al., 2010]. Accordingly, Pepsinogen levels and their ratio are decreased in corpus atrophy, accompanied by elevated G-17. G-17 level also gives indication of gastric acid secretion, being low with high acid output and high when the stomach is acid-free (due to PPI treatment or AG). In antrum atrophy, G-17 is low and does not respond to protein stimulation (lack of G-cells).

In our series, using GP testing, the HS and NHS groups were distinguished with high accuracy. According to the test results, the serum levels of all 4 biomarkers were significantly different between the two groups, remarkably, the marker of inflammation (PgII) was almost three times higher in the NHS group.

As described by many authors, HP is the key causative factor of severe gastric pathology, including peptic ulcer disease and gastric cancer [Agreus et al., 2012; Shrestha et al., 2014; Nomura et al., 1991; Peleteiro et al., 2014]. In the study cohort (Publication II), the prevalence of HP (66%) in candidates for bariatric operation was significantly higher than that reported for bariatric patients in many previous studies from Belgium, Finland and the USA (3.4–17%) [D`Hondt et al., 2013; Peromaa-Haavisto et al., 2013; Gomez et al., 2014], but similar to that reported from Greece and Brazil (53–66%) [Papavramidis et al., 1996; Assef et al., 2015; Dietz et al., 2012]. In the Estonian population, HP prevalence is closely associated with the birth cohort [Oona et al., 2004; Vorobjova et al., 2000]: HP has become more rare among younger generations. In our bariatric cohort, the high HP prevalence is in accordance with the data of earlier studies (56–69%) involving the same birth cohorts of general population in Estonia [Oona et al., 2004; Vorobjova et al., 2000].

Because HP is associated with severe clinical sequelae [Agreus et al., 2012; Shrestha et al., 2014; Nomura et al., 1991; Peleteiro et al., 2014], its eradication is indicated [D`Hondt et al., 2013] and leads to regression of the inflammatory process in the gastric mucosa and significantly reduces the risk for its known complications at the population`s level. Indeed, the reported preoperative endoscopic findings (hiatal hernia, 16–25%; esophagitis, 13–30%) from geographic regions with low HP prevalence [D`Hondt et al., 2013, Peromaa-Haavisto et al., 2013, Gomez et al., 2014], as well as from the the high prevalence regions [Papavramidis et al., 1996; Assef et al., 2015; Dietz et al., 2012], are consistent with similar morbidity in our cohort (hiatal hernia, 29%; esophagitis, 21%). Chronic inflammation of the stomach mucosa was detected in 75% (49/65) and atrophy in 6.2% (4/65) of the patients. As expected, gastric diseases (gastritis, 65.1%; AG, 16.7%) are more frequent in regions [Papavramidis et al., 1996, Dietz et al., 2012] with high HP prevalence, like Estonia, as compared with the low-prevalence regions (gastritis, 9.1–28%; AG 0.9%) [D`Hondt et al., 2013; Peromaa-Haavisto et al., 2013; Gomez et al., 2014].

Most of the patients in the NHS group had HP-related gastritis without atrophy. In such cases, gastroscopy is optional if the patient requests it [Agreus et al., 2012]. Gastroscopy is mandatory only in cases of suspected AG or in patients with sustained symptoms. In the NHS group, only four patients had moderate AGA which requires regular monitoring by endoscopy to disclose the eventual progression and increased risk of gastric cancer [Nomura et al., 1991; Benotti et al., 1995]. Of these four AGA cases, only one was clearly confirmed and another one was suspected on the basis of biomarker testing. In the other two cases, AGA was only confirmed with biopsy. In GastroPanel, the G -17 values were within normal limits, implicating that abundant G-cells were still present to sustain the normal G-17 output. Most likely, these cases represent patchy mucosal atrophy instead of a diffuse disease. It is not well established how such patchy atrophy behaves in the long run, and whether regular endoscopic monitoring is indicated or whether biomarker testing is sufficient. It is likely that the gastric mucosa in these patients can significantly recover after HP eradication, while inflammation symptoms diminish or disappear and the process of mucosal atrophy can be arrested, as reported earlier by many authors [Benotti et al., 1995; Lehmann et al., 2000; Storskrubb et al., 2008; Dixon et al., 1996].

In our series, AGA detected by biomarkers was rare, which has been shown earlier [Graham et al., 2006]. A recent meta-analysis of the published GastroPanel literature confirmed that the test works better for detection of AGC (PgI, PgI/PgII ratio) compared to AGA (G-17). A simple explanation is that low G-17 levels can result from two distinct causes: AGA and high acid output [Agreus et al., 2012; Syrjänen K., 2016; Sipponen et al., 2005]. No one biomarker that is regulated by more than one trigger can be a highly specific indicator among the others [Syrjänen K., 2016]. To make distinction between these two (AGA, high acid output), it is mandatory to test G-17 after protein

stimulation (G-17s). Failure to increase G17s output implicates lack of G-cells and presence of AGA [Syrjänen K., 2016].

Another explanation for the rarity of AGA in our series could be the relatively young age of the patients. In fact, GastroPanel was not primarily designed for testing bariatric surgery patients, but rather for diagnosis and screening of elderly patients with AG and for screening for the increased risk of gastric cancer [Teleranta-Keerie et al., 2010]. However, bariatric surgery can be safely performed also in patients aged 60 years or older [Giordano et al., 2015; Eisenberg et al., 2022]. In this sub-group, the potential role of the gastric biomarker test can be particularly important, as the incidence of atrophy and gastric cancer increases with age. Furthermore, using the biomarker test, we could easily diagnose almost all HP-infections and administer timely treatment to diminish the risk of AG and gastric cancer.

There was also one false positive "panatrophy" (according to GP) in our series, while histologically only superficial HP related gastritis was confirmed. Rather, this fact could be related to technical issues.

In patients with AG, follow-up EGDS is still needed. Thus the sleeve gastrectomy method (SG) would be preferable, because routine EGDS after bypass operation is unfeasible. In large series of operated patients, however, practically no post-operative problems have been reported for the bypass group [Safatle-Ribeiro et al., 2007; Csendes et al., 2012; Csendes et al., 2006]. Only a few case reports are available on postoperative cancer [Escalona et al., 2005; Khitin et al., 2003; Ribeiro et al., 2013].

Regarding the use of the normal GP profile as a surrogate for the healthy stomach (HS), 22/65 subjects were categorised into this group according to its criteria. Clinically, 20 of them were asymptomatic, had no history of abdominal complaints, and only 2 had reflux symptoms. On EGDS, only minor abnormalities were detected that were considered clinically insignificant: non-HP gastritis, mild or moderate degree esophagitis, or gastric mucosa erosions. It is clear that management of these disorders does not require a delay in elective surgery, nor is it a contraindication for operation [Parikh et al., 2016]. In 4 cases, esophagitis (LA grade A/B) was found to be associated with hiatal hernia, and 2 of these subjects reported reflux complaints. According to international consensus [Anderson et al., 2008; Parkin DM., 2004], for patients with upper abdominal complaints, endoscopic investigation is indicated. In patients with symptomatic esophagitis, the recommended surgical procedure could be gastric bypass rather than sleeve gastrectomy. Although the opinions on the use of sleeve gastrectomy in esophagitis are controversial [Hawasli et al., 2016], the probability of complicated esophagitis has been shown to increase postoperatively [Melissas et al., 2015; Graham et al., 2006]. Such cases respond poorly to medical treatment [Stenard et al., 2015], despite the fact that a major portion of the gastric corpus is resected, which results in significant reduction in parietal cell mass and a decline in acid output. Current conditional recommendation from the Interdisciplinary European Guidelines on Metabolic and Bariatric

Surgery suggest not to perform LSG in patients with severe GERD symptoms and/or severe esophagitis [Di Lorenzo et al. 2020].

In a study of Sipponen et al. the authors demonstrated that low G17b levels in the general population are a marker of high basal acid output, which in turn predisposes to gastric acid reflux and esophagitis [Sipponen et al., 2005]. In this series, however, we failed to find correlation between esophagitis and low G17b levels, as only one out of the 4 patients in the HS group and 2/10 in the NHS group showed G17b levels below the cut-off value. Although some studies have obtained results similar to ours [Monkemuller et al., 2008; Peitz et al., 2011], there are also reports on such correlation between G-17 and esophagitis [Goni et al., 2015].

In the light of the above data, it is evident that in symptomatic esophagitis, endoscopy plays a role also in guiding the selection of the surgical method (i.e., preferring gastric bypass over gastric sleeve), which is crucial to ensure optimal treatment outcome. In our series, 3 asymptomatic patients in the HS group had, despite the normal marker profile, erosions in the stomach (antrum), with a Lanza score of less than 4 (i.e. not severe). Recently, some authors have reported gastric erosions in bariatric surgery patients [Fernandes et al., 2016] and others have reported them also in asymptomatic volunteers in population studies, more frequently in HP-negative than HP-positive subjects [Lehmann et al., 2000]. Although the cause of such erosions may be multifactorial, all 3 patients in our study took several medications known to damage the gastric mucosa. Yet the erosions seen in the HS group can be considered clinically insignificant: the patients were asymptomatic, and no complications like hemorrhage were found on EGDS. Accordingly, we cannot consider minor erosions in patients with the normal biomarker profile as an indication for changing treatment practises in these bariatric surgery patients.

Our data demonstrate that gastric biomarker test can definitely help select asymptomatic patients (20/22 in this series) with minor but clinically non-significant gastric mucosa alterations for whom preoperative endoscopic investigation can be safely replaced by non-invasive biomarker test. Endoscopy should only be reserved for symptomatic patients to confirm the diagnosis and to opt for the surgical method, as has been pointed out earlier [Anderson et al., 2008; Parkin DM., 2004].

Regarding NHS patients, the rationale should be the same as for HS patients: those with reflux complaints should undergo endoscopic investigation to confirm the diagnosis and to plan possible preoperative treatment.

Endoscopic findings in bariatric surgery patients can be highly variable [Fernandes et al., 2016]. To avoid postoperative complications, including ulcer [Fernandes et al., 2016], it is important to evaluate the patients pre-operatively to detect (by using GP) [Agreus et al., 2012] and eradicate HP infection. Although there were no cases of ulcer disease in our material, these steps are always important in this special group of patients. In the case of suspected peptic ulcer, EGDS is essential; the same applies to patients with a family history of gastric cancer.

The results of our study confirm that the normal biomarker profile in the test is an excellent surrogate for the healthy stomach, and this non-invasive test could replace EGDS in the pre-operative management of bariatric surgery patients. Indeed, using biomarker test, it could have been possible to avoid EGDS in 20/22 patients in the HS group, i.e, in 31% (20/65) of all bariatric patients in our cohort. These asymptomatic patients with the normal biomarker profile are at a very low risk to develop a clinically significant disease in the gastric mucosa, including peptic ulcer and gastric cancer [Agreus et al., 2012; Sipponen et al., 1993].

As expected, both operative methods (LSG, 73% and LRYGB, 65%) yielded satisfactory 1-year %EWL results, with the data being comparable to relevant literature data (Perrone et al., 2017; McNickle AG et al., 2017). Similar results (LSG, 67% and LRYGB, 63%) of EWL% at 2 years postoperatively can be found in our other study (Publication I).

Little is known about the status of the gastric mucosa and possible changes in gastric biomarkers after bariatric operations. Our studies demonstrate that marked dynamic changes in the biomarker profile can be detected in both operated groups (LRYGB and LSG) during 2- year follow-up after bariatric surgery (Publications III, I).

A major decrease in PgI and PgII values was noted in the LSG patients already during the first postoperative days; the values stabilised after 3 months and remained low for at least one year postoperatively. In 82% of the patients, PgI was below the reference value (30 μg/L), normally indicating severe atrophy of the corpus mucosa in a non-operated stomach. Similar results (reduction in PgI levels) have been shown in an earlier study in peptic ulcer patients 1 year after vagotomy and after Billroth I gastric resection (the antrum and a segment of the gastric corpus being removed). In that study none of the gastric ulcer patients developed atrophy of the gastric corpus mucosa although they showed a pronounced decrease of Pg I in comparison with its preoperative level [Peetsalu et al., 1990].

In the LRYGB patients, the increase of PgI and PgII level during the first postoperative days was of short duration and can be attributed to operation related trauma. Starting from the first postoperative month until the end of the first postoperative year, the PgI values for about 60% of the patients were below the reference range. Similar results can be found in a study by Sundbom et al. [Sundbom et al., 2007].

The dynamics of G17f differed between the two study groups. In the case of LSG, its values were higher than the reference values in 61% of the patients at postoperative day 1, however, by the end of the first postoperative year, the proportion of such patients had stabilised at 32%. In the LRYGB patients, the levels of G17b were low. As no protein stimulant reached the gastric antrum, there was no response of G17s to any stimulant and the levels of G17s were as low as the levels of G17b.

Our study demonstrates dynamic changes in the serum levels of the studied gastric biomarkers after operative treatment during a 1-year follow-up period. The changes are primarily caused by alterations induced by the operation and were more pronounced in the LSG than in the LRYGB patients. As confirmed by biopsies, these changes in biomarker levels did not coincide with any morphological changes in the gastric mucosa during one year of follow-up. Similar results in the mean values of the gastric biomarkers can be seen at 2 years postoperatively in both the LSG and LRYGB groups (Publication I). Given that both studies were conducted on the same (bariatric) population, one can anticipate that changes in the gastric biomarker levels will be stable at least during a period of 1–2 years postoperatively in case there is no weight regain.

In the absence of a detectable mucosal pathology, the obtained biomarker findings suggest „reduction“ and „down-regulation“ in the function of the gastric corpus in particular; one could also implicate the status of hypoacidity in fasting gastric remnants after both operations. Accordingly, in the LSG patients, the PgI and PgII levels decreased and the G17b levels increased. Such a rapid change can be explained by the fact that most of the gastric corpus in the LSG patients was resected and hence the number of PgI producing cells decreased significantly, as suggested in our Publication I [Sillakivi et al., 2013]. By resecting a substantial proportion of the stomach corpus and fundus, also a huge parietal cell mass is removed from the corpus, resulting in a marked reduction in gastric acid output. The antral G cells respond quickly to the decrease in acid output and boost their G17 output. A similar effect on G17 values is seen also in patients during PPI treatment: hypoclorhydria leads to the stimulation of G17 production [Agreus et al., 2009]. Increased G17 production is the normal function of the atrophy-free gastric antral mucosa. Acid secretion is reduced, although the histology of the corpus biopsies remains unaffected. Because of hypoacidity, there may arise the risk for malabsorption of micronutrients (iron, calcium, etc) and vitamin-B12 [Schubert ML., 2014; Schubert ML., 2015; Sipponen et al., 2003].

Unlike in LSG, nothing is removed from the abdominal cavity during LRYGB operation, where a small pouch created from the proximal part of the stomach is anastomosed to the small bowel leaving 90% of the primary stomach out of food passage. In our studies, changes in the gastric biomarker levels are less pronounced in this group as compared to the LSG patients. The increase of PgI and PgII in the first few postopetrative days is most likely caused by irritation (inflammation) due to surgical manipulation. At the late follow-up of the LRYGB patients, the decrease of PgI and PgII may be explained by the resting status of the stomach, as proposed also earlier [Sundbom et al., 2003]. Also, fast food passage from the small pouch to the small intestine can even further reduce secretion in the bypassed stomach.

We noted a decrease of PgI from month 1 onwards, followed by stable, abnormally low values in 60% of the patients after one year. At the 1-year follow-up visit, the G17 values among 11% of the LRYGB patients were above the upper normal limit. It can be speculated that this is the result of a reaction

due to vagotomy which decreases gastric acid secretion in the bypassed stomach.

The small pouch cannot produce PgI in adequate amounts. The reason is not atrophy of the pouch or remnant itself but the insufficient mucosal mass involved in PgI production in the pouch. At the same time, acid secretion in the bypassed stomach may still take place, since G17b is mostly within normal limits and not increased (as should be the case with the acid-free stomach). In the bypassed stomach, however, acid secretion takes place in a blind loop and does not counteract the risk of malabsorption. In fact, the risk of postoperative malabsorption must be even higher after LRYGB than after LSG.

The mean PgII values in both operation groups changed at first parallel with the mean values of PgI, being lower at the end of the first postoperative month and increasing thereafter. By the end of year 1, the initial reduction had diminished to only 30% and 14% of the mean preoperative values in the LSG and LRYGB groups, respectively. It should be noted that PgII is produced not only in the corpus but also in the other parts of the stomach (antrum, fundus, duodenum). The above changes can be explained by mucous neck cell hyperplasia, which has been demonstrated in animal experiments [Arapis et al., 2015].

In the present setting, the gastric mucosal pathology in the LSG group, both preoperatively and at 1-year follow-up, was mainly related to HP-associated chronic (non-atrophic) gastritis.

Alterations were more pronounced in the antrum than in the corpus, which is consistent with earlier data [Onzi et al., 2014]. Atrophic gastritis, which invariably affects the gastric biomarker profile, was diagnosed in only one patient preoperatively but was no more detectable at 1-year follow-up. This resolution can be attributed to successful HP eradication therapy, which is well documented in the literature [Zhou et al., 2003; Benotti et al., 1995; Lehmann et al., 2000]. Another option, which is hard to exclude, is that atrophy in the preoperative biopsies was patchy and the right focus was missed in the follow-up biopsies.

Although we do not have postoperative gastrobiopsies from the LRYGB group, then according to the literature, no substantial changes in the mucosa have been found either in the gastric pouch or in the gastric remnant (Csendes et al., 2006; Safatle-Ribeiro et al., 2007; Csendes et al., 2012).

According to our study, the preoperative gastric biomarker levels are not associated with %EWL at 1-year follow-up, which precludes the prospect to predict weight loss, or to select an appropriate operation type preoperatively on the basis of the GP biomarker profile. The GP was designed for screening the atrophy of gastric mucosa in asymptomatic subjects and should not be used as a screening test for gastric cancer. Similarly, as suggested by Marchesi et al., GP test is of limited value in predicting morphological changes in the stomach mucosa after bariatric surgery, as is shown also in this study, due to the simple reason that any such morphological changes are practically non-existent [Marchesi et al., 2017]. In patients who underwent bariatric surgery, the value

of the gastric biomarkers lies in their applicability in the follow-up period. GP test gives an opportunity to follow up the gastric status after surgery, and in LSG patients, to estimate the severity of functional disturbance in acid output.

Monitoring stomach physiology after bariatric surgery is clinically important, because the sequelae caused by resection or bypass may interfere with the welfare and health of the operated subjects in the long run. A hypoacidic stomach remnant, which is common after LSG, and bypassing of food passage in LRYGB, may impair digestion, as well as absorption of vitamins (eg. vitamin-B12), micronutrients and some pharmaceuticals [Schubert ML., 2014; Schubert ML., 2015].

Further studies will provide more knowledge and indices for specifying whether changes in these functions are clinically relevant or not and whether they are related, for example, to malabsorption of vitamins, micronutrients and medicines in the long term.

Our study also has some weaknesses. The number of patients is too small for using sensitivity and specificity in order to compare histology findings and biomarkers preoperatively. A limitation of our study is that in one study group the knowledge of the preoperative plasma biomarker levels and stomach histology is lacking. This study does not report surgical complications. Another weakness of our study is the lack of postoperative gastric biopsies in the LRYGB group. According to other studies, however, there are no major histopathological changes either in the pouch or in the bypassed stomach during the first postoperative years [Csendes et al., 2006; Safatle-Ribeiro et al., 2007; Csendes et al., 2012). Also, it should be taken into account that the population is limited, as the study was conducted at a single center and most of the patients were residents of only the southern and eastern parts of Estonia. The full benefits of the non-invasive biomarker screening of bariatric surgery patients pre- and postoperatively can only be established in larger cohorts, with participants from different populations and with different prevalences of HP-infection.

Future perspectives

- The studied biomarkers could hypothetically enable to abandon invasive preoperative EGDS among some patients. It must be considered that in recent years the indications for endoscopy have broadened, mostly due to the problems caused by postoperative GERD.
- At present, the biomarkers that we used in our work did not enable to predict the operative success nor aid the selection of operation method. Further studies are needed to better select patients for optimal treatment.
- Nowadays there are no good guidelines for choosing between different treatment options (medical vs surgical treatment).
- Currently surgical treatment is superior, but presumably proportion of medical treatment will increase in the future.
- New medications are promising, but studies are still in progress. Long term outcomes and persistency of results over time have major importance.

8. CONCLUSIONS

1. The results of our study confirm that the normal biomarker profile in GP test is an excellent surrogate for the healthy stomach. In asymptomatic obese patients with the normal biomarker profile, this non-invasive test could replace preoperative EGDS. According to the results of our study, preoperative EGDS could have been avoided in 31% of the patients of the study group (20/65).
2. The changes in the biomarker levels are stable for at least 2 years postoperatively. Biomarker profile in SG and RYGB group are quite similar one and two years after surgery.
3. Our study demonstrates that significant (dynamic) changes occur in the biomarker profile after bariatric surgery. The changes are primarily caused by operation and do not indicate pathological changes in gastric mucosa. The changes are more pronounced in the LSG patient group.
4. Preoperative gastric biomarker levels do not correlate with %EWL at 1-year follow up, indicating that the operative success in %EWL cannot be predicted on the basis of the preoperative GP marker profile.

9. SUMMARY IN ESTONIAN

Mao biomarkerid ja nende dünaamika kui väheinvasiivne meetod mao seisundi hindamiseks bariaatrilise kirurgia patsientidel

9.1. Sissejuhatus

Viimastel aastakümnetel on ülekaalulisuse ja rasvumise levimus oluliselt suurenenud ning sellest on saanud tõsine terviserisk nii arengu- kui arenenud riikides. Tänapäeval on rasvumine muutunud tervishoiu prioriteediks üle kogu maailma [Ogden et al., 2006; Benotti et al., 1995; Williams et al. 2015; Kelly et al. 2015]. Maailma Tervishoiu Organisatsiooni (WHO) andmetel oli 2016. aastal rohkem kui 1,9 miljardit maailma täiskasvanud elanikkonnast ülekaalulised, neist omakorda üle 650 miljoni olid rasvunud [WHO, 2021]. Ülekaalulisus ja rasvumine on gastroösofageaalse reflukshaiguse, ösofagiidi, söögitorulahisonga, söögitoru Barret metaplaasia, söögitoru adenokartsionoomi ja *Helicobacter pylori* riskifaktoriteks. Ülekaalulistel patsientidel esineb eelpool nimetatud patoloogiaid 2–3 korda sagedamini kui normaalkaalulistel [Gerson LB., 2009].

Paralleelselt rasvunute arvu suurenemisega on pidevalt tõusnud bariaatriliste operatsioonide arv maailmas, kuna raskekujulise rasvumise korral on kirurgiline sekkumine ainus tõhus ja kestvat toimet pakkuv ravimeetod [Flum et al., 2007; Azagury et al., 2011].

Varasemad uuringud haavandtõve patsientidel vagotoomiate ja mao osaliste resektsioonide järgselt on näidanud, et operatsioonid maol tekitavad muutusi nii jääkmao limaskestal kui ka mao sekretsioonivõimes [Peetsalu et al., 1990]. Siiski on teadmised bariaatriliste operatsioonide järgselt tekkinud mao limaskesta muutuste osas piiratud.

Bariaatriliste patsientide pre- ja postoperatiivses käsitluses on mao seisundi hindamise ja patoloogiate tuvastamise kuldseks standardiks olnud seedetrakti ülaosa endoskoopiline uuring koos mao limaskesta biopsiatega. Samas puudub paljudel autoritel üksmeel asümptomaatilistele patsientidele teostatava rutiinse endoskoopilise uuringu vajalikkuse osas [Parikh et al., 2016; Csendes et al., 2007; D`Hondt et al., 2013; Almazeedi et al., 2013; Gerson LB., 2009].

Viimastel aastakümnetel on järjest enam populaarsust kogunud vereproovil baseeruv biomarkerite testpaneel (“seroloogiline biopsia”), mis aitab väheinvasiivset meetodit kasutades diagnoosida mao funktsionaalseid muutusi ja limaskesta patoloogiaid, sh. *Helicobacter pylori* infektsiooni ja limaskesta atroofiat [Agreus et al., 2012]. Eelpool nimetatud testpaneel põhineb neljal maospetsiifilisel biomarkeril (Pepsinogeen I ja II (PgI, PgII), Gastriin-17 (G-17)), *Helicobacter pylori* antikeha (HPAK)), mille väärtuste põhjal saab eristada 8 erinevat markerite profiili [Agreus et al., 2012; Syrjänen et al. 2019].

Informatsioon bariaatrilise operatsiooni järgselt tekkinud muutuste kohta mao füsioloogias omab olulist kliinilist tähendust, kuna operatsioonil teosta-

tavate resektsioonide ja möödajuhtimistega kaasnevad muutused on püsivad ja kestavad aastaid. Arvestades bariaatriliste operatsioonide arvu kasvu, oleks "väheinvasiivse" meetodi kasutamine mao limaskesta seisundi hindamiseks pre- ja postoperatiivselt väga hea lahendus, eriti patsientide puhul, kellele on tehtud möödajuhtiv operatsioon.

Meie uurimistöö eesmärgiks oli välja selgitada, kas biomarkerite testi abil oleks võimalik vältida invasiivse endoskoopilise uuringu tegemist bariaatrilisele operatsioonile minevatele asümptomaatilistele patsientidele, ning kirjeldada mao biomarkerite profiili muutust mao vertikaalse resektsiooni (SG) ja maost möödajuhtiva operatsiooni (RYGB) järgselt. Muutused biomarkerite profiilis võiksid anda uut informatsiooni maovähendusoperatsiooni tõttu tekkinud võimalike komplikatsioonide ja kaebuste kohta ning aidata läbi viia patsiendipõhist ravi (sh. asendusravi) konkreetse operatsioonitüübi järgselt.

9.2. Uuringu eesmärgid

1) Selgitada välja, kas väheinvasiivse seroloogilise biomarkerite testi kasutamine aitaks preoperatiivselt vältida invasiivset endoskoopilist uuringut plaanilisele bariaatrilisele operatsioonile minevate patsientide hulgas.
2) Uurida mao limaskesta funktsiooni ja happe sekretsiooni bariaatrilise operatsiooni järgselt – millised muutused toimuvad mao biomarkerite profiilis kahe aasta jooksul peale operatsiooni.
3) Hinnata, kas postoperatiivselt tekkinud muutused mao biomarkerite profiilis on seotud operatsioonist tingitud anatoomiliste muutustega või on nende põhjuseks mao limaskesta patohistoloogilised muutused; samuti hinnata, kui kiiresti tekivad muutused biomarkerite tasemes postoperatiivselt.
4) Hinnata, kas mao biomarkerite pre- ja postoperatiivsed väärtused korreleeruvad ühe aasta liigse kehakaalu langusega.

9.3. Uuritavad ja meetodid

Antud uuring baseerub 105 patsiendi andmetel, kellele teostati ajaperioodil 2008–2016 Tartu Ülikooli Kliinikumi kirurgikliinikus maovähendusoperatsioon. Uuringusse kaasatud patsiendid olid vähemalt 18-aastased, vastasid bariaatrilise operatsiooni kriteeriumitele (kehamassiindeks (KMI) >40 või >35 koos rasvumisest põhjustatud kaasuva haigusega) ning kes andsid nõusoleku uuringus osalemiseks. Uuringusse ei kaasatud alla 18-aastaseid patsiente, kriteeriumitele mittevastavaid patsiente ning neid, kes ei soovinud uuringus osaleda.

Uuringus osalenud patsiente intervjueeriti, neil võeti vereanalüüsid *Gastropanel* testi jaoks ning teostati endoskoopiline uuring koos mao limaskesta biopsiate võtmisega eri uuringugruppidel erinevatel ajaperioodidel. Kõikidele uuringu patsientidele teostati kas laparoskoopiline SG või laparoskoopiline RYGB.

Intervjuu läbiviimine ning füüsikaliste parameetrite (pikkus, kaal, KMI, vööümbermõõt) fikseerimine toimus enne vereanalüüside võtmist ja endoskoopilist uuringut ning enne operatsiooni (Publikatsioon II), samuti postoperatiivsel jälgimisperioodil 1, 3, 12 kuu möödudes (Publikatsioon III) ja 2 aastat peale bariaatrilist operatsiooni (Publikatsioon I).

Vereanalüüsid *Gastropanel* testi jaoks võeti preoperatiivselt ning seejärel postoperatiivselt 1., 3. päeval, 1., 3., 12. kuul ning 2 aasta pärast (erinevates uuringu gruppides).

Endoskoopiline uuring koos mao limaskesta biopsiate võtmisega teostati preoperatiivselt (Publikatsioonid II ja III) ja 12 kuud peale bariaatrilist operatsiooni (ainult SG grupi patsientidel) (Publikatsioon III).

Uurimustöö esimeses etapis uuriti preoperatiivselt maospetsiifilisi biomarkereid ja mao limaskesta biopsiaid. *Gastropanel* testi tulemuste alusel jagati patsiendid kahte gruppi: terve magu (HS) ja haige magu (NHS). Mõlema grupi biomarkerite testi tulemusi võrreldi otseselt mao limaskesta biopsiate vastustega (Publikatsioon II).

Uurimustöö teises etapis võrreldi maospetsiifiliste biomarkerite dünaamikat kahe erineva operatsioonigrupi (SG ja RYGB) vahel kahe operatsioonijärgse aasta jooksul (Publikatsioonid III ja I).

9.4. Tulemused

Gastropanel testi tulemuste alusel kuulusid 22 patsienti HS gruppi ning 43 patsienti NHS gruppi. Biomarkerite (PgI, PgII, PgI/PgII ja IgG) väärtused erinesid kahe grupi vahel märkimisväärselt ($p<0,001$). *Gastopanel* testi tulemuste ja mao limaskesta biopsiate vastuste omavaheline kokkulangevus oli väga hea (Kappa=84,6%).

Mao biomarkerite tasemes ilmestusid postoperatiivselt kahe operatsioonigrupi (SG ja RYGB) vahel suured erinevused. SG grupis langes PgI tase kiiresti peale operatsiooni ning 1 aasta möödudes oli PgI tase märkimisväärselt madalam võrreldes operatsioonieelse tasemega ($p<0,0001$). Samasugune (madal) PgI tase esines ka kaks aastat peale operatsiooni. RYGB grupis langes PgI tase alates esimesest postoperatiivsest kuust ning esimeseks postoperatiivseks aastaks oli toimunud märkimisväärne langus võrreldes operatsioonieelse tasemega ($p<0.0001$), kusjuures madal tase püsis ka kahe aasta möödudes.

Võrreldes operatsioonieelsete väärtustega toimus ühe aasta möödudes PgII ja PgI/PgII tasemes märkimisväärne langus mõlemas operatsioonigrupis (SG grupp, PgII $p<0,0006$; PgI/PgII $p<0,0001$).

Basaal-G17 tase tõusis SG grupis esimese ja teise aasta lõpuks, samas kui RYGB grupis basaal-G17 tase langes 12 kuu möödudes 28% võrreldes algväärtusega.

SG grupis täheldati ühe ja kahe aasta möödudes operatsioonist stimuleeritud G17 (G17s) normaalset taset (vastus stimulatsioonile >3 pmol/l) vastavalt 40% ja 100% juhtudest. RYGB grupis oli G17 vastus stimulatsioonile adekvaatne vaid vastavalt 7,4% ja 25% juhtudest.

Postoperatiivsed gastrobiospiad (SG grupis) kirjeldasid kroonilise gastriidi esinemist 92% patsientidest, atroofiat ei esinenud.

Pre– ja postoperatiivsete (ühe aasta) ega preoperativsete/postoperatiivsete (ühe aasta) biomarkerite tase ei korreleerunud kummaski operatsioonigrupis 1 aasta liigse kehakaalu languse protsendiga.

9.5. Järeldused

1) Meie uuringu tulemused kinnitavad, et *Gastropanel* testi normaalne biomarkerite profiil peegeldab hästi terve mao seisundit, mistõttu võiks antud väheinvasiivne test asümptomaatilistel rasvunud patsientidel asendada preoperatiivset endoskoopilist uuringut. Käesoleva uuringu tulemuste alusel oleks preoperatiivne endoskoopiline uuring olnud välditav 31% uuringu patsientidest (20/65).
2) Muutused biomarkerite tasemes püsivad stabiilsena vähemalt kaks aastat peale operatsiooni. SG ja RYGB grupis toimunud muutused biomarkerite tasemes on sarnased 1. ja 2 aasta möödudes operatsioonist.
3) Meie uuringute tulemused näitavad, et bariaatrilise operatsiooni järgselt toimuvad lühikese aja jooksul (juba päevadega) märkimisväärsed muutused biomarkerite profiilis. Nende põhjuseks on operatsioon ise, mitte aga mao limaskesta patoloogia. Muutused on rohkem väljendunud SG patsientide grupis.
4) Preoperatiivne mao biomarkerite tase ei korreleeru esimese postoperatiivse aasta liigse kehakaalu languse protsendiga, mistõttu nende alusel ei saa ennustada operatsiooni edukust kaalulanguse aspektist.

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