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INTEGRATED STUDY MASTER'S THESIS

Obesity Treatment With Intragastric Balloon

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ABSTRACT – *English/Lithuanian*

English

The following thesis compares and investigates the clinical outcomes of endoscopic intragastric balloons implanted for usually six months, with non-invasive intragastric balloons such as the common Allurion balloon. The Allurion intragastric balloon has a treatment duration of usually four months. Over the whole world, the obesity rate is rising, so this study evaluates the minimally invasive treatment outcomes for patients who are not able or fit enough for bariatric surgery or don´t want to due to complications. This thesis mentioned endoscopic placed intragastric balloons like the Orbera, ReShape Duo and Spatz3, which are implanted and explanted with an endoscope in general anaesthesia. These endoscopically placed intragastric balloons usually managed to achieve a higher total body weight loss from 14 to 18%, combined with an excess weight loss of 65%. These balloons usually show higher complication and intolerance rates, such as nausea, early balloon explantation or gastric ulcers. Compared to these, non-invasive balloons such as the Allurion or Obalon Balloon can be implanted without endoscopy or general anaesthesia. Usually, the patients can swallow the balloons by themselves without bigger complications. Their total body weight loss is a bit lower, with 10 to 14%, but usually, these balloons are well tolerated by the patients and show complications and adverse reaction rates of 0.5%. In general, this thesis shows the importance of comparing different intragastric balloons of similar treatment durations to improve the clinical outcome of each patient. This thesis shows and summarises different outcomes of various intragastric balloon systems and shows that endoscopic balloons achieve a little bit higher weight loss outcome, but non-invasive balloons will offer a good option for patients who prefer safe, simplified and short-term treatment without any risk of endoscopy and general anaesthesia. Selecting the right balloon for each patient depends on the individual BMI, weight loss goal and personal preference.

Lithuanian

Šiame darbe lyginami ir tiriami endoskopinių intragastrinių balionų, implantuojamų paprastai šešiems mėnesiams, klinikiniai rezultatai su neinvaziniais intragastriniais balionais, tokiais kaip įprastas Allurion balionas. Allurion intragastrinio baliono gydymo trukmė paprastai yra keturi mėnesiai. Visame pasaulyje didėja nutukimas, todėl šiame tyrime vertinami minimaliai invazinio gydymo rezultatai pacientams, kurie negali arba nenori atlikti bariatrinės operacijos dėl komplikacijų. Šiame darbe minimi endoskopiniu būdu implantuojami intragastriumo balionai, tokie kaip Orbera, ReShape Duo ir Spatz3, kurie implantuojami ir šalinami endoskopu, taikant bendrąją anesteziją. Šiais endoskopiškai dedamais intragastriniais balionais paprastai pavykdavo pasiekti

didesnį bendro kūno svorio sumažėjimą nuo 14 iki 18 % kartu su 65 % viršsvorio sumažėjimu. Šie balionai paprastai sukelia daugiau komplikacijų ir netoleravimo atvejų, pavyzdžiui, pykinimą, ankstyvą baliono eksplantaciją ar skrandžio opas. Palyginti su jais, neinvaziniai balionai, pavyzdžiui, Allurion arba Obalon balionas, gali būti implantuojami be endoskopijos ar bendrosios anestezijos. Paprastai pacientai gali patys nuryti balionus be didesnių komplikacijų. Jų bendras kūno svorio sumažėjimas yra šiek tiek mažesnis - 10-14 %, tačiau paprastai šiuos balionus pacientai gerai toleruoja, o komplikacijų ir nepageidaujamų reakcijų dažnis siekia 0,5 %. Apskritai šis darbas rodo, kaip svarbu palyginti skirtingus intragastrinius balionus su panašia gydymo trukme, siekiant pagerinti kiekvieno paciento klinikinius rezultatus. Šiame darbe parodyti ir apibendrinti skirtingi įvairių intragastrinių balionų sistemų rezultatai ir parodyta, kad endoskopiniais balionais pasiekiama šiek tiek geresnių svorio mažinimo rezultatų, tačiau neinvaziniai balionai bus geras pasirinkimas pacientams, kurie pageidauja saugaus, supaprastinto ir trumpalaikio gydymo be jokios endoskopijos ir bendrosios anestezijos rizikos. Kiekvienam pacientui tinkamo baliono parinkimas priklauso nuo individualaus KMI, svorio metimo tikslo ir asmeninių pageidavimų.

Keywords: Endoscopic Intragastric Balloon (IGB) Therapy, Non-endoscopic Intragastric Balloons, Obesity-Related Weight Loss Interventions, Comparative Analysis of Weight Reduction Methods, Gastrointestinal Devices for Obesity Treatment, Gastrointestinal Satiety Mechanisms, Minimally Invasive Obesity Therapies

Table of Content

List of Abbreviations

Abbreviation	Full Term
BMI	Body Mass Index
CE	Conformité Européenne (European Conformity)
EWL	Excess Weight Loss
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon-Like Peptide-1
IGB	Intragastric Balloon
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
SAE	Serious Adverse Event
T2DM	Type 2 Diabetes Mellitus
TBWL	Total Body Weight Loss
WHO	World Health Organisation

Topic: Comparison of weight loss outcomes after different types of intragastric balloons - endoscopic (6 months) vs non-invasive (4 months).

1. INTRODUCTION

Obesity is a common disease in our modern world. It is defined as excessive fat deposits that can affect general health. In general, overweight and obesity are diagnosed through the body mass index (BMI), calculated as weight in kilograms divided by height in square meters. The BMI is a standard tool, while the obesity classification varies by age and sex in paediatrics, such as infants or children.[1]

According to the WHO, adults are defined as overweight when the body mass index reaches or exceeds 25kg/m2. Obesity in the general population is defined as a BMI or higher equal 30. [2]

1.1 Background

Obesity is one of the biggest public health crises of the 20th and 21st centuries, with its prevalence reaching epidemic proportions worldwide. The World Health Organisation (WHO) exhorts that the general obesity rate has grown three times since the year 1980. Over 650 million adult patients were classified as obese in 2016. The situation in Europe is alarming, with the WHO reporting that 23.3% of men and 22.1% of women in the European Union were obese in 2014. The rising trend is evident across all age groups. The general obesity rate rises while affecting younger populations like children and teenagers.

The general health problems of obesity are profound and multifaceted. Obesity is a leading risk factor with an elevated risk of developing chronic diseases.[4] These diseases can include the most widespread diseases in obese people, like type 2 diabetes mellitus and cardiovascular diseases. Cardiovascular diseases can be strokes, severe hypertension or coronary artery diseases. Obesity increases the rate of certain cancers, including cancers of the endometrium, breasts or colon. Through increased BMI, diseases, including those in the skeletal system, can develop, such as osteoarthritis. Diseases, including the respiratory system, are also likely in obese people. This can include problems like obstructive sleep apnea.

All these comorbidities can significantly reduce the quality of life and life expectancy and impose substantial burdens on general healthcare systems due to increased medical costs and the need for long-term management of chronic conditions.

1.2 Impact on Society and Economics

Obesity not only has direct and chronic health consequences but also social and economic impacts. Studies found that general healthcare costs due to the treatment of obesity-related diseases are much higher than usual. It was also found that obesity is highly associated with unemployment and absenteeism. In Europe, the additional healthcare costs due to obesity are estimated to be between 3-7% of total health expenditures. In addition, obesity can lead to social discrimination and mental health problems, which can contribute to conditions such as depression or anxiety.

1.3 Weight Loss Strategies

One of the most important and effective management programs is the early prevention of unwanted weight gain from body fat. Physical activeness is one of the most essential components of a weight-loss strategy for adults who are overweight but otherwise in good health. It is also helpful to use behaviour and lifestyle modifications. The primary goal of these modifications is to increase physical activity and minimise caloric intake by changing individual eating lifestyles. All these methods can be helpful for some people, but not for all. These changes can be challenging for most people, and many won't achieve significant weight loss. Pharmacological treatment and medications like Orlistat could be a good option for those people. These medications are long-term approved, but each patient must remember that all these medications can have individual side effects.[5]

One of the newest obesity medications is semaglutide. These medications are called Ozempic and Wegovy. They are glucagon-like peptide (GLP-1) receptor agonists. Ozempic is an approved medication for the general enhancement of glycaemic improvements in people with type 2 diabetes mellitus. It is a subcutaneous injection-type medication and helps in reducing the risk of cardiovascular diseases. It can reduce the risk of cardiovascular mortality, strokes or heart attacks. It activates the GLP-1 receptors, which are mainly located in the gut, pancreas, and central nervous system. It also enhances general insulin secretion, which responds to elevated blood glucose levels after each meal. It can also slow the general gastric emptying and reduce the patient's general appetite.[6]

Another semaglutide subcutaneous injection medication is Wegovy. This medication is combined with a low-calorie diet and physical activity. It is usually used for patients with a body mass (BMI) index greater than 30 kg/m2. If the patient has comorbidities such as hypertension, it could also be used for a body mass index (BMI) of 27kg/m2. It is also approved for paediatric patients older than 12 and an average BMI over the 95^{th} percentile.[7]

Another subcutaneous injection medication is called liraglutide. They are called Saxenda and Victoza. Victoza is a 1.8mg daily subcutaneous injection of liraglutide and is used as one of the possible treatment options for patients with type 2 diabetes. Saxenda is a 3.0 mg daily subcutaneous injection which is used for patients with chronic weight management problems and a BMI of 27 kg/m2 or higher.

Liraglutide is a modified form of the GLP-1 peptide, nearly 100% similar in its amino acid sequence. It acts like the semaglutides, such as Wegovy and Ozempic. The main difference between liraglutide and semaglutide is their half-life. Liraglutide requires daily injection due to its 13-hour half-life. Semiglutide can be injected once weekly because of its 7-day half-life.[8]

Another new medication is called Mounjaro. It is a tirzepatide and an incretin agonist of the glucose-dependent insulinotropic polypeptide (GIP). Also, it is an agonist of the GLP-1. It is an approved medication for glycaemic control in type 2 diabetes (T2DM) patients. Usually, the patient will inject a single subcutaneous dose once a week. Mounjaro is a relatively well-tolerated medication with a low risk of hypoglycaemia and cardiovascular contraindications.[9]

1.4 Surgical options

For patients with severe obesity, surgical interventions have a high effectiveness rate. The main invasive surgeries, like the gastric banding, Roux-en-Y bypass and sleeve gastrectomy, can also improve severe weight loss and good results in the improvement of obesity-related comorbidities. Only adults with a BMI greater than or equal to 40 without severe medical conditions or adults with a BMI of 35-39.9 with at least one comorbidity are suitable for bariatric surgeries.

The Roux-en-Y gastric bypass is a surgical weight loss procedure in patients with a BMI of 40 or higher. It includes creating a pouch from the patient's stomach. This newly created small pouch will be directly connected to the patient's small intestine. Swallowed food will directly go into this newly formed pouch and then into the small intestine. By that, most parts of the food will bypass the stomach.[10]

Another surgical procedure can be gastric banding. This surgery is performed in patients with a BMI of 40 or higher or patients with a BMI equal to 35 or higher but with an additional overweight disease. This bariatric surgery involves inserting a band made of silicone around the upper part of the patient's stomach. It is called a lap band. This band reduces the stomach capacity and slows the food through the stomach. With this surgery, the patient should eat less and lose weight. Gastric banding is a surgery that is reversible and adjustable.[11]

An also effective procedure is the sleeve gastrectomy procedure. It is one of the most popular bariatric surgeries nowadays. The general indications for this surgery are like those of the other two mentioned surgeries. In this surgery, the surgeon will remove nearly 80% of the patient's stomach, leaving a small part shaped like a tube. Usually, this tube will have the size and look of a banana. The patient's stomach is limited in size, leading to less food the patient can consume and following weight loss.[12]

1.5 Intragastric balloons

Besides bariatric surgeries, a less invasive and effective alternative is the intragastric balloons for patients with severe obesity. Intragastric balloons are one of the possible options for the treatment of obesity and overweight in patients who are not suffering from advanced obesity, in patients who may be suitable for surgical treatment but are not willing to undergo surgery, or where surgical invasion is considered too risky due to the patient's existing premature and therapeutic state. Intragastric balloon treatment can also be combined with other treatments, such as drug therapy with mandatory dietary and lifestyle adjustments – for a greater long-term weight loss effect.

In this procedure, each patient will get the balloon placed in the stomach using an endoscope. After that, the balloon will be filled with a saline solution or simple gas. The placed balloon gives the patient a feeling of fullness and satiety. Through that, the food intake of each patient will be reduced, and immediate weight loss will occur. Usually, most of them will be removed endoscopically after 6 months. The balloons used the most for 6 months are Orbera, ReShape Duo, MedSil, and End-Ball. Intragastric balloons have been a part of obesity treatment strategies since the 1980s, but recent advancements have significantly improved their effectiveness and safety. Through these advancements, patients can choose intragastric balloons, which are not placed endoscopically. One of them is called the Allurion program. It is the world´s first weight loss item where no anaesthesia, endoscopy and surgery are needed. It is placed in a 15-minute meeting by swallowing the device and passes naturally after 16 weeks.[13]

1.6 Indications and Contraindications

Indications for intragastric balloon surgery are different between Europe and the US for each patient. In the guidelines, the patient must undergo different weight management strategies before the treatment with the intragastric balloon. The threshold in Europe is a BMI of 27kg/m2, but in the US, the threshold is 30kg/m2. Intragastric balloons can be considered an early intervention therapy in European patients with a BMI of 27-35 kg/m2. Usually, these early interventions can prevent or even treat obesity-related illnesses which could occur in the future. Intragastric balloon treatment is

the first treatment of choice for patient who don´t comply with the high BMI criteria for surgery.[14]

As in every medical procedure, contraindications can appear. A general medical history and examination by a doctor must be conducted in every patient. This is necessary to identify possible contraindications for intragastric balloons. Attention should be given to previous gastrointestinal disorders. This kind of Contraindications can be gastric surgery, hepatic diseases, upper gastrointestinal bleeding of other serious medical conditions. [15]

1.7 Efficacy and Outcomes

Many clinical studies have demonstrated the efficacy of intragastric balloon surgeries in obese patients. The patients achieve a significant weight loss from 6 to 15% of their total body weight in six months. Through lifestyle changes, most patients only can lose 1 to 5% of their total body weight. If intragastric balloon therapy was one of the primary therapies without bariatric surgeries in the past, the average weight loss is around 11.5 kg. This weight loss can prevent obesity comorbidities like diabetes 2, arterial hypertension or dyslipidaemia. The long-term outcomes depend on the patient's willingness to lifestyle modifications and follow-up care.[16]

1.8 Advantages and Limitations

In general, intragastric balloons have many advantages over common bariatric surgeries. These include their minimally invasive procedure, low cost, and reversibility. Intragastric balloons can help people lose weight that can´t be operated on with bariatric surgeries. Of course, the duration of intragastric balloons is limited, and most will only stay for 6 months in the patient's stomach. Still, with an adaptation of eating habits, each patient can remain within normal weight limits.

1.9 Conclusion

Nearly all intragastric balloon therapies are effective and have minimally invasive weight loss and management options. These therapies offer an alternative to more complicated and invasive bariatric weight loss procedures. Endoscopically placed and non-invasive intragastric balloons have shown a high efficacy in weight loss. Significant differences between weight loss strategies can be found in mechanisms, durations, and clinical outcomes. Usually, balloons placed endoscopically provide more weight loss than non-invasive intragastric balloons. That's why, usually, these balloons will stay longer in the patient and have the possibility of larger volumes. Non-invasive intragastric balloons significantly reduces the risk of complications compared to invasive

intragastric balloons. Anyway, non-invasive intragastric balloons have lower overall weight outcomes.

The following literature review of these two weight loss approaches will provide a general insight into which strategy will better suit which patient profiles. Besides the total weight loss, this review will also consider factors such as safety, patient adherence and overall long-term weight outcomes. By examining available literature, this thesis aims to offer a clinical overview of weight loss outcomes after different types of intragastric balloons - endoscopic (6 months) vs non-invasive (4 months).

2. METHODOLOGY AND LITERATURE SELECTION

This thesis is written in a systematic literature review style, which aims to evaluate and compare different obesity treatment strategies. It mainly focuses on intragastric balloon therapy, but also GLP-1 receptor agonists, and other surgical methods play a crucial role. This review follows the PRISMA guidelines for a transparent and methodologically stringency. Studies were picked out through a structured search in databases like PubMed or Google Scholar.
The general search strategy was used with specific keywords such as “Endoscopic Intragastric Balloon (IGB) Therapy, Non-endoscopic Intragastric Balloons, Obesity-Related Weight Loss Interventions, Comparative Analysis of Weight Reduction Methods, Gastrointestinal Devices for Obesity Treatment, Gastrointestinal Satiety Mechanisms, Minimally Invasive Obesity Therapies”. The studies consisted mainly of adult human research and outcomes related to weight loss and body mass index. After the general screening of the studies, the most relevant studies were analysed for an overview of current therapeutic methods.
The data search revealed 734 different papers. After removing the duplicates of 126, 608 were left. Of these, 402 were excluded due to non-important criteria such as non-English publications, case reports and animal studies. A total of 206 were left to check for eligibility. Based on the criteria for this thesis, 98 studies were included in the final version.

3. OBESITY AND MANAGEMENT

3.1 Epidemiology

The number of patients affected by obesity has increased over the last few years. One of the four primary behavioural factors which cause death from non-communicable diseases is an unhealthy eating lifestyle.[17] Obesity has become a serious medical condition characterised by excessive body fat that affects the organ systems and overall well-being. It is a serious global public health

problem which leads to many deaths all around the world.[18] States around the world must act on this current situation due to the significant impact obesity has on the whole population.[19]

3.2 Levels and trends of overweight and obesity in the EU

The general amount of people with obesity is usually higher in wealthier countries around the world. The WHO Global Health Observatory indicates that general obesity is more popular than in any other country worldwide except the Region of the Americas. Nearly 59% of the older population live with general overweight/obesity. In 50 out of 53 states of the European Union, more than half of the adults live with general overweight or obesity.[20] In general, the overweight and obesity levels are higher among the male population than the females. Among the male population, the overweight and obesity levels are nearly 63%. In the female population, the percentage of overweight people is almost 54% in the WHO European region. In some countries, the predominance is nearly 70% in males. Almost 25% of the adults in the European region are obese. In 49 out of 53 countries, one-fifth of adults live with obesity. In contrast to overweight, obesity is more seen in the female population of the WHO European Region. Obesity is frequent in 24% of females and 22% of males in nearly 50% of the countries. The most severe average levels of obesity and overweight are seen in the south and east of Europe. The educational gap in Europe between countries can also be seen regarding overweight and obesity. Countries with lower educational possibilities have higher obesity prevalence.[21]

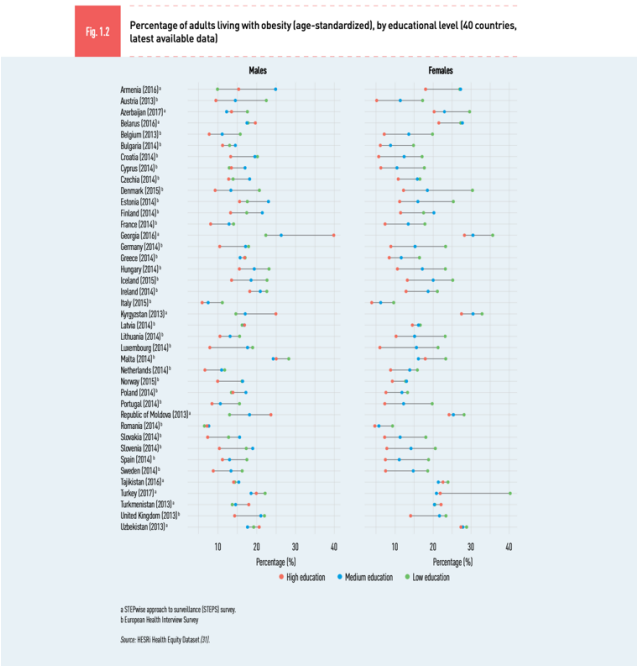


Fig 1. Percentage of adults living with obesity (age-standardized, by educational level (40 countries, latest available data) [22]

The fast increase in levels of overweight and obesity is a serious distress in adults. In the WHO European the prevalence of overweight and obesity increased by nearly 21% in the decade up to 2016. Since 1975, the percentage of obesity in these countries has risen by nearly 150%. The rise in the rate of overweight, including obesity, was a bit less in the past decades. In the ten years before 2016, it rose by 8%, and since 1975 by 50%. An alarming sign is a continuous rise since voluntary targets for non-communicable diseases were adopted in 2013. Only a few member states are making progress in meeting the targets to stop growing rates of overweight and diabetes. [23] Not only among the adult population, obesity and overweight are present problems, but also among children and adolescents. In 2020, obesity was a serious issue in the WHO European Region. Overweight and obesity are affecting nearly 4.5 million children under 5 years. In this age group, 4.5 million children are overweight or obese, which represents 8% of children in this age.[24] This is not only true in the age group up to the age of 5, but the increased prevalence of overweight can also be seen between the ages of 5 and 19. It increased in the male population nearly three times between 1975 and 2016, and almost two times in the female population of the same age.

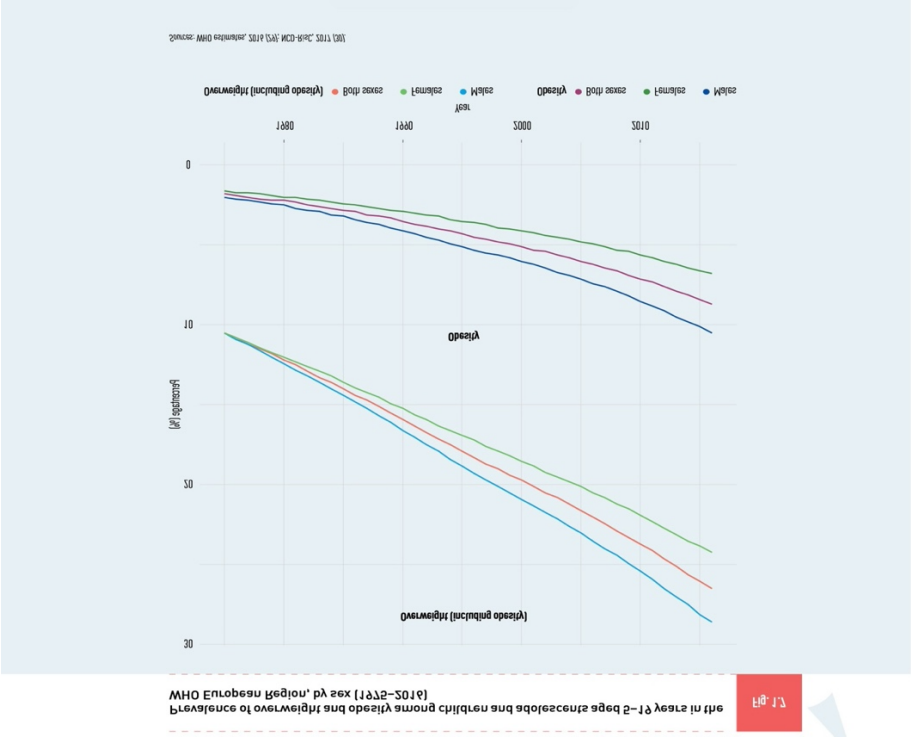


*Fig 2. Prevalence of overweight and obesity among Children and adolescents aged 5-19 years in the WHO European Region, by sex (1975-2016) [*25]

4. HEALTH CONSEQUENCES RELATED TO OBESITY

Overweight and obese people are at an increased risk of obesity-related diseases. Many of these diseases are frequently related to an increasing BMI. Individuals with severe obesity are found to have a shorter life expectancy than people of normal weight. It is nearly five years shorter compared to those with a normal BMI. Across the WHO European Region, every year, almost 1.2 million deaths are related to overweight or obesity. This number represents 13% of total deaths. This ranks it in the fourth place. Elevated blood pressure, unhealthy diet and tobacco consumption are in third place. Overweight and obesity are not only directly related to death but also are a common reason for severe disability syndromes.

The obesity-related complications are an additional point to the fact that adipose tissue functions as a metabolically active organ. This adipose tissue contains fat cells called adipocytes, which release and receive hormones. These substances are called adipocytokines. Adipocytokines can function in a systemic or local action. These actions include the general glucose, lipid metabolism, cell development or oxidative stress. All these actions induce health complications in obese people. The organs in the abdominal cavity of the human body are covered and surrounded by visceral fat. Visceral fat has a higher health influence on the human body than fat. Its higher biological activity is usually attributed to a higher density and blood flow, mainly because of the portal vein. This leads to a higher concentration of fatty acids, leading to the human liver.[26]

Research from 2022 shows that the harmful effects of being overweight and obese are not only the consequences of a too high percentage of fat in the human body but also because of its ability to respond to changes and the general plasticity declines. The consequences of these changes are that the bodies of overweight or obese people can adapt less to changes like ageing or weight fluctuations. As fat plasticity declines due to ageing and being overweight, time after time, it stops the function of producing bodily cues. In such cases, the expansion of adipose tissue exceeds the capacity of the vascular supply. This lack of oxygen damages fat cells and accumulates cells that cannot divide themselves. The following issues could be insulin resistance, inflammation and even total cell death.[27]

Overweight and obesity are linked to many conditions that can elevate the general risk of CVDS. These conditions can include atherosclerosis, severe Hypertension, insulin resistance, dyslipidaemia and increased coagulability. Excess body weight leads to a high coronary artery disease rate, which can represent the two forms of CVD-related death. Fat accumulation around the abdomen is a more serious risk indicator for both diseases than total body fat. In general, this shows that abdominal and visceral fat are more dangerous.[28] Overweight and obese people have a higher risk of different

types of cancer. Abdominal obesity is highly connected to endocrine-related malignancies.[29] Most common Cancers that develop in people who are overweight and obese include breast, colorectal, pancreatic, gallbladder, liver, kidney, gastric, thyroid, ovarian and blood cancers. In obese people, the risk of metastatic cancer is also increased.[30]

Obesity is not only connected to chronic conditions like cardiovascular diseases and cancers. It is also linked with a high risk of health complications and chronic conditions. These conditions include non-alcoholic fatty liver disease and type 2 diabetes. But also, musculoskeletal and respiratory diseases. Additionally, obese people often face social problems like bullying, which can lead to depression.

The general health impacts of obesity significantly burden the European health systems in terms of lost productivity and treatment costs. Obese people tend to have nearly 30% higher healthcare costs than normal-weight people. In 2014, 8% of healthcare costs were related to obesity in the European Union Member States. A general report from the Organisation for Economic and Cooperation and Development (OECD) reveals that an average of 8.4% of the annual health budget will be spent on managing overweight and obesity. This statistic shows the importance of treatment plans for the prophylaxis and reduction of general overweight and obesity.[31]

5. CONVENTIONAL AND SURGICAL WEIGHT LOSS OPTIONS

The control of general obesity and following side effects in modern society has improved in the near past. This has led to many options, such as dietary, pharmacological, and surgical strategies.

5.1 Dietary therapy

A deficit of daily kilocalories each human needs per day can achieve general weight loss. Each human adult has an energy demand per kilogram of approximately 22 kcal. There are many ways to achieve a general energy deficit.

Table 1. Summary of dietary interventions for weight loss – continue next page

Diet	Principles	Mechanisms of action	Variants
Low calorie diet	800–1600 kcal/day	Negative energy balance (net deficit of calories)	Cambridge diet Weight Watchers Nutrisystems diet Intermittent

Diet	Principles	Mechanisms of action	Variants
			Fasting Biggest Loser SlimFast Jenny Craig
Very low-calorie diet	200–800 kcal/day		
Low calorie diet: meal replacement	Pre-cooked low-calorie meals		
Low fat diet	Fat accounts for <30% of energy intake	Negative energy balance achieved by reduction of dietary fat, which is the most energy-dense macronutrient (9 kcal/g)	LEARN Ornish Rosemary Conley
Low carbohydrate diet	Carbohydrate intake <130 g/day	Negative energy balance achieved by reduction of dietary carbohydrates (3.75 kcal/g) Mobilisation of glycogen jstores and associated water loss Ketogenesis	Atkins South Beach Zone.
Very-low carbohydrate diet	Carbohydrate intake <60 g/day		
High protein diet	Protein accounts for >30% of energy intake	Increased satiety leading to reduced passive overconsumption of other macronutrients, thus achieving a lower energy balance	
Mediterranean-style diet	High intake of fruits, vegetables, grains; moderate intake of fat (mostly mono-unsaturated) and dairy (mostly cheese), reduced intake of meats (fish and poultry in preference to red meat)	Lipid reduction Lowering of oxidative stress and improved endothelial function Anti-inflammatory effects Gut microbiota changes	

[32]

The macronutrients - Fat, Carbohydrates, and Protein achieve 9, 3.75, and 4 kilocalories/gram. The most calorie-dense macronutrient is fat and is readily absorbed, yet it is the least satiating. Due to these characteristics, it is often one of the primary targets in weight loss strategies. Recent data on

low-fat diets showed a significant weight loss to reference diets. On average, with a reduction of 5.41 kg. Compared to high–fat diets, low-fat diets did not show better weight loss outcomes.[33]

Low-carb diets lead to a quicker weight loss reduction than low-fat diets, with nearly 3.5kg lost over six months. This effect is related to glycogen and water loss, after which the weight loss rate usually slows down.

Proteins are known for their high satiety value. They are common in high-protein diets to minimise the passive overconsumption of macronutrients that are less satiating and provide more energy. Some databases show that high-protein diets don't have such a significant effect in limiting total body weight. Mostly, the effect is too small and has limited clinical relevance. This evidence shows the different factors that impact macronutrient composition on weight loss outcomes. In each approach, individual preferences and metabolic reactions play an important role.[34]

5.2 Pharmacotherapy

Newer guidelines recommend using pharmacological treatment options combined with a reduction in calories and physical activity to help and improve weight loss. Pharmacological treatments are usually prescribed for patients with a BMI over 30kg/m2 or patients with additional risk factors with a BMI of 27kg/m2. One of the most essential factors is discontinuing the treatment if the patient has not achieved a weight reduction of nearly 5%.

One of the most known pharmacological treatment options is Orlistat. Orlistat is one of the older pharmacological medications for the treatment of obesity, but it is still a very effective method. The mechanism of action involves inhibiting the lipase, which is the enzyme for breaking down fats into molecules. By blocking the pancreatic lipase, the absorption of up to 32% of dietary fat is prevented.[35] Orlistat can have common side effects such as faecal urgency, oily stools and incontinence, which can often be solved by following a low-fat diet and taking Orlistat with meals or within an hour. Some databases of 33 controlled trials reported an average weight reduction of 2.2kg, with a treatment range from 2 months to 3 years.[36] In addition to weight loss, orlistat reduces cholesterol and triglyceride levels. The 4-year double blind RCT XENDOS Trial found out that patients treated with orlistat lost significantly more weight than the placebo group. (-10.6kg vs. -6.2 – 1 year; -5.8kg vs -3.0kg – 4 years). This led to a 37.3% reduction in the risk of type 2 diabetes and cardiovascular side effects.[37]

Another popular pharmacological agent is called Liraglutide. It is a glucagon-like peptide (GLP-1) agonist which can be injected daily by subcutaneous injections. GLP-1 is a gastrointestinal hormone which is produced while eating. It is an essential factor in glucose metabolism and helps to regulate the appetite. Its main effects include slowing gastric emptying and helping to control blood sugar

while suppressing the appetite. Side effects of Liraglutide are gastrointestinal problems and rare cases of acute pancreatitis. Databases show that the average weight reduction of Liraglutide is about 3.2 kg. Liraglutide has a positive effect with a reduction of 1% in HbA1c levels and a decrease in cholesterol and blood pressure. [38] Liraglutide has been approved and validated through the Safety and Clinical Adiposity-Liraglutide Evidence clinical trial (SCALE).

The outcomes of these studies show a significant weight loss compared to placebo – (-8.4kg vs. -2.8kg) over one year, with even more participants losing more than 5% of weight.[39]

A mixed pharmacological supplement is Naltrexone/Bupropion (Mysimba). It is a combined fixed-dose medication to support weight loss alongside dietary and general life changes. Currently, it is not advised by some guidelines because the effectiveness is not known. Originally, Naltrexone was used to treat alcohol and opioid dependency. Bupropion is an antidepressant medication that increases dopamine and noradrenaline levels in the brain. Combined supplements suppress appetite by affecting and suppressing the hunger centres in the hypothalamus. In a three-phase study involving 1.742 participants, the combined supplement showed a weight reduction of 6.1% compared to 1.3% of placebo. Side effects of supplements are nausea, headaches and constipation.[40]

One of the newest pharmaceutical medications is tirzepatide, called Mounjaro. Tirzepatide is a new-generation glucagon-like peptide-1 receptor (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) drug. The clinical efficacy in treating overweight patients with type 2 diabetes mellitus (T2DM) is prominent A huge clinical trial, including 12 different studies and nearly 10.000 patients, compared general weight loss using tirzepatide with a placebo group. This meta-analysis presented a statistically significant weight loss reduction compared to the placebo group. The other group achieved an average weight loss of 9.81kg compared to the placebo group, with a difference of 1.05 kg when compared to GLP-1 receptor agonists and 1.05kg compared to insulin. In this data analysis all three tirzepatide doses 5mg, 10mg and 15mg showed significant weight reduction compared to the placebo, GLP-1 and insulin groups. In general, compared to the other groups, tirzepatide has higher complication rates then the other groups. In this data analysis, a high number of patients discontinued the treatment due to mild side effects. Tirzepatide showed a low complication rate of hypoglycemia compared to the other groups. Adverse effects like nausea, diarrhoea, vomiting and loss of appetite were significantly higher than the adverse effects of the placebo and insulin groups. All these side effects were like other subcutaneous injection medications such like GLP-1 medications.[41]

5.3 Intragastric ballons

Besides pharmacological and lifestyle methods, intragastric balloons have been an effective intervention to prevent obesity. Since 1985, intragastric balloons have been a standard method for patients with severe obesity. Intragastric balloons are silicone balloons filled with saline. These balloons will be inserted into the stomach of the patient endoscopically and will stay there for up to 6 months. Intragastric balloons are a good alternative option for weight loss for patients who don't want to do bariatric surgery or who aren`t allowed to. These balloons diminish the stomach volume, so the patients eat less until the feeling of satiety takes place.[42]

5.4 Bariatric surgeries

These surgeries are considered when all other interventions have been unsuccessful and failed. Compared to non-surgical interventions, bariatric interventions show the highest effectiveness in weight loss. One of the most significant obesity studies is the Swedish Obesity Study (SOS). It provides observational data about the impact of bariatric surgery. The study shows a higher weight loss degree in the surgical patients than in the non–surgical group. It also indicates that bariatric surgeries have a better long-term outcome in diabetes resolution and weight loss than pharmacological methods alone.

The latest NICE guidelines for bariatric surgery recommend for patients who meeting the following criteria:

- BMI ≥ 40kg/ m2 or higher
- BMI of at least 35 kg/m2 with co-morbidities that may benefit from weight reduction
- BMI between 30–34.9 kg/m^2 in patients with T2DM
- Other conservative and medical weight loss options have been attempted but failed.

The most common types of bariatric surgeries are:

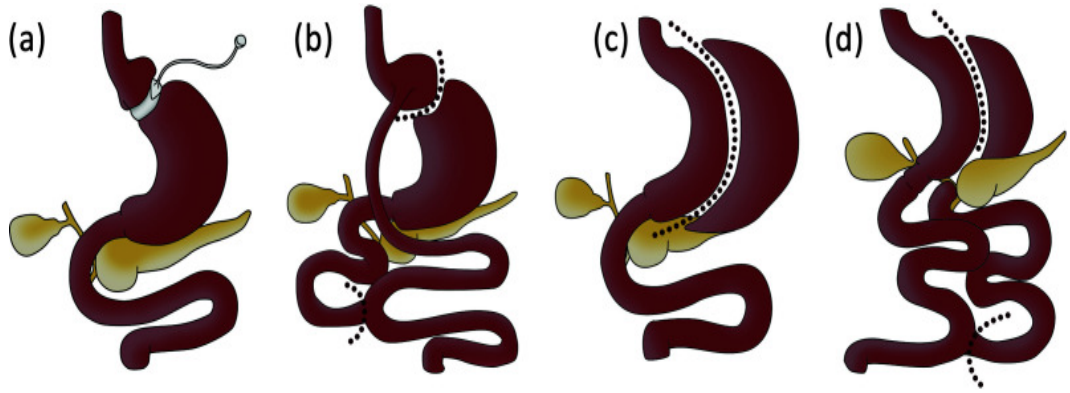


Fig 3. Bariatric surgeries are schematic. (a) Adjustable gastric banding. (b) Roux-en-Y gastric bypass. (c) Sleeve gastrectomy. (d) Bilio-pancreatic diversion with a duodenal switch. [43]

Laparoscopic adjustable gastric banding

This bariatric surgery involves placing a flexible silicone band around the upper stomach to from a pouch. By decreasing and compressing the lumen, the band gets decreased in its functional stomach capacity and slows down the possible food passage. This allows a detailed calibration of the lumen which results in a controlled food intake while maintaining satiety with less amount of food intake. This serves as the primary mechanism. The band's tightness can be regulated with saline injections via a port. Statistically, laparoscopic adjustable gastric banding leads to a weight loss of up to 55% within two years after the surgery. It also helps to improve and rectify other health problems related to overweight or obesity. In 74% of cases, it can cause diabetes remission, in 54% hypertension, in 40% dyslipidaemia, and 94% sleep apnoea. Some complications include oesophageal pouch dilation (11%), band slippage (7.9%) and gastroesophageal reflux.[44]

Roux-en-Y gastric bypass

In the Roux-en-Y bypass, the surgeon divides the upper section of the stomach, forming a small proximal pouch that restricts the general food intake. At the jejunal level, the small intestine is divided, and the distal end of the small intestine is reconnected at the new stomach pouch—the food then bypasses the portion of the small intestine, resulting in reduced absorption of nutrients. In this procedure, the distal part of the stomach is reconnected to the proximal small intestine. It also bypasses a portion of the digestive tract, which allows the enzymes to mix with the food. This procedure is usually performed laparoscopically and achieves significant weight loss, with studies that show nearly 73% excess weight loss in the first year. The Roux-en-Y gastric bypass is an effective method in resolving comorbidities, with a remission rate of 95% for diabetes, 85% for hypertension, 80% for dyslipidaemia and 95% for sleep apnoea. [45] The mortality in this surgery is lower in laparoscopic approaches than in open surgery approaches. The most frequent complications include anastomotic leaks, which occur in 3-5% of cases and internal bowel herniation, which has an incidence of around 3.1%. [46]

Sleeve gastrectomy

Sleeve gastrectomy is the only bariatric surgery where 80% of the stomach is removed. After removal, a small sleeve remains. This small sleeve reduces motility and lowers the volume of food entering and exiting the stomach. Lower calorie intake is the result. This bariatric surgery is also primarily performed laparoscopically, leading to weight loss up to 70% in one year. Sleeve gastrectomy also lowers the risk of comorbidities related to overweight and obesity, such as

diabetes 86%, dyslipidaemia 83%, sleep apnoea 91% and hypertension 82%. This procedure has a low mortality rate, with leakage one of the most prominent complications, occurring in 2-3% of cases.

Biliopancreatic diversion with duodenal switch

This irreversible intervention consists of a two-step surgical approach, with an option of a open or laparoscopic intervention. The first step is a standard sleeve gastrectomy with which a small, narrow, tube-shaped stomach pouch is created. The surgeon divides the small intestine into two parts in the second step. The first place is proximal after the pylorus, and the second is distal, around 2.5m before the ileocecal valve. The distal segment is reattached to the duodenum. The residual middle part is surgically connected to the ileum, approximately one meter before the ileocecal valve.[47] Biliopancreatic diversion with duodenal switch can achieve up to 73% weight loss with results of up to 8 years. Like the Roux-en-Y bypass, it works via restrictive and malabsorptive mechanisms and helps improve comorbidities like type 2 diabetes mellitus.[48] Compared to other bariatric surgeries, this surgery is more complex and shows higher risks, such as perioperative anastomotic leakage, which usually occurs in 3-4% of cases. Also, an internal bowel herniation is a rare complication with a rate of 2-7%. [49]

6. Intragastric Balloons: Mechanisms and Types

As a therapeutic intervention, the treatment with bariatric surgery provides the best success rates for patients with severe obesity. Nevertheless, patients face restrictions when becoming candidates for surgical interventions. Bariatric surgeries like Roux-en-Y, Sleeve gastrectomy, Laparoscopic banding and Biliopancreatic diversion with duodenal switch usually require a BMI of at least 35kg/m2 with comorbidities or a BMI criterion for severe obesity with at least 40kg/m2.[50]

These parameters leave an intermediate group of patients who can’t be operated on but also do not respond well or fail to other medical therapies against their overweight. These patients also seek safe, fast-reacting, minimally invasive weight-loss therapy, like intragastric balloon therapy.

Intragastric balloon placement offers an invasive weight loss option and is an effective intervention for obese patients. A balloon filled with saline, or air is inserted into the patient’s stomach using an endoscopic procedure. The balloon functions as a space-occupying device and promotes satiation. The gastric capacity of an adult patient is approximately 1.2 L, but an obese patient can stretch the stomach capacity up to three times.

In most patients, satiety is achieved with a filled balloon of around 400 ml. [51] A key mechanism is slowing gastric emptying, which thereby facilitates weight reduction.

An important factor is the lifestyle changes every patient must complete, before and after the surgery, to achieve and maintain long-term weight loss.

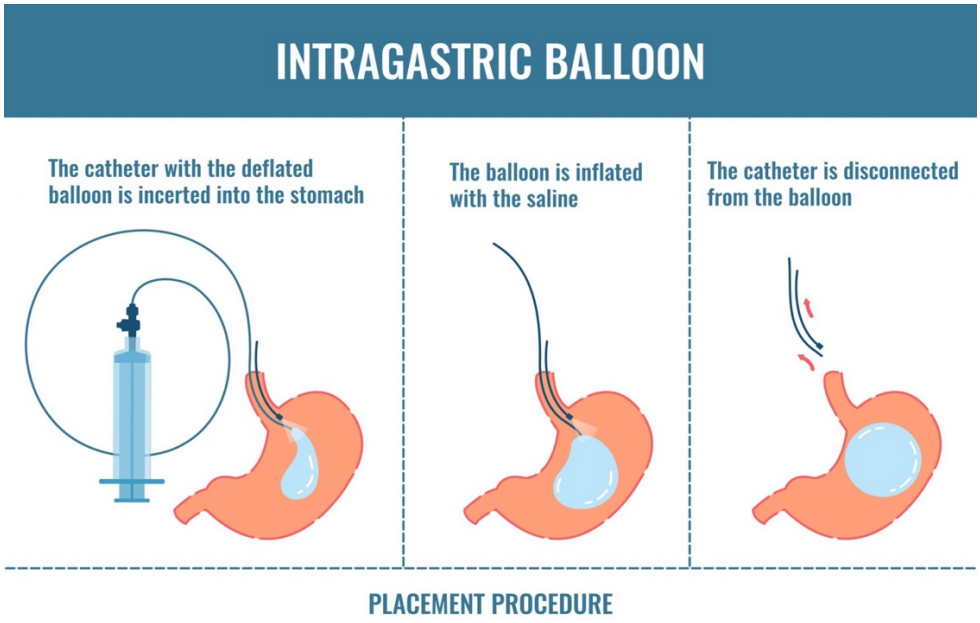


Fig 3. Intragastric balloon [52]

6.1 Pathophysiology

In general, intragastric balloons promote a feeling of satiation. It uses a restrictive mechanism to encourage weight loss. By reducing the stomach's capacity with an intragastric balloon and occupying one-third of the stomach's volume, the capacity to hold food is decreased dramatically. This leads to a limited caloric intake. However, the intragastric balloon also has limited effectiveness. It can only work effectively if the patient is willing to do diets and work on daily exercise modifications. A key aspect of intrasgatric balloons is their impact on the neuro-humoral axis. It plays a critical role in regulating satiety and body weight.[53]

The brainstem combines hormonal and nerve signals to regulate the function of the body. These signals derive from the gut and adipose tissue. The brainstem circuity provides essential signals for saturation, satiation and hunger. Hormonal and psychological factors influence mechanical stimuli such as gastric distention. The stomach undergoes distention after ingesting food and sends saturation signals through the parasympathetic afferent fibres. Brainstem nuclei regulate tonic activity and induce the gastric relaxion during meals. Some neuroimaging studies show the differences in brain response, comparing physiological distention caused by nutrient intake and

mechanical distention induced by intragastric balloons. The nutrient-based distention is related to regions associated with satiety. Compared to that, the mechanical distention by an intragastric balloon engages brain areas related to pain. During food intake, the pain-processing regions of the pain neuromatrix become downregulated. This physiological mechanism ensures an adequate food intake despite gastric distention. Through that mechanism, the body´s energy supply is balanced with sensory feedback.[54]

This process can explain the complications in the first week after the intragastric balloon is placed in the patient's stomach and the feeling of satiety after food intake. MRI findings indicate that sugary drinks don't affect the cortical pathways combining the craving regulation. This can lead to less benefit for patients with an intragastric balloon with a high intake of liquid calories.[55] Ghrelin is a key hormone for regulating satiation and hunger.

Ghrelin is an amino peptide. It is primarily produced in the gastric fundus and plays a crucial role in weight loss. Ghrelin activates eating, carbohydrate metabolism, and energy homeostasis and stimulates growth hormone release from the pituitary gland. Binding to the growth hormone secretagogue receptors (GHS-R) activates its appetite-stimulating effects. Besides its role in appetite-stimulating effects, ghrelin promotes general lipogenesis and adipose tissue deposition.[56]

The hunger hormone ghrelin works by increasing the appetite feeling while slowing down the digestion. This affects the body blood sugar control.t The relationship between Ghrelin and intragastric balloons is still unclear. Studies show that caloric intake may be a necessary part of ghrelin secretion.

It also shows that the mechanical effects of intragastric balloons alone are insufficient to reduce ghrelin levels in the patient's plasma. Restrictive process of intragastric balloons and hormonal factors are not the only factors relating to weight loss. Gastric emptying is also essential for weight loss after inserting the intragastric balloon. Three months after placing the intragastric balloon, studies show a significant delay in gastric emptying of solid food and liquids.

This fact positively affects general weight loss. A key question remains: Do intragastric balloons effects stay throughout the treatment process and period? Some subjective reports indicate a diminished feeling of hunger after the intragastric balloon placement, but these effects will subside after two months after the insertion. [57]

Slower gastric motility is usually connected to the saline or fluid-filled balloons. When the balloon gets filled with fluid, it will sink to the distal part of the stomach portions. As a result, the gastric emptying of liquids and solid food is prolonged. A prolonged stomach emptying results in a more extended phase of satiation. The mechanisms combined in intragastric balloon treatment are

multifactorial. Firstly, it involves gastric distention due to the fluid-filled balloon's restrictive effect. Secondly, it affects the hormones through the ghrelin signalling, and thirdly, the general prolonged gastric emptying time.

All these combined physiological effects help in weight reduction over the treatment period.[58]

7. TYPES OF INTRAGASTRIC BALLOONS

7.1 Endoscopic balloon – 6 months

Currently, many intragastric balloon variations are used in clinical practice in case of weight reduction. All these intragastric balloons differ in methods of insertion and removal. They also differ in fluid volume and duration of staying in the patient's stomach. All gastric balloons run like a bezoar. They take the stomach space and stretch it. This creates a feeling of satiety and reduces food intake, which leads to weight reduction.[59]

Orbera IGB

The Orbera intragastric balloon, named the BioEnterics intragastric balloon, was one of the first intragastric balloons of the new generations. It was approved in 1991 following the Tarpon Springs Consensus. Today, it is one of the most endoscopically placed intragastric balloons used worldwide. All other intragastric balloons following the Orbera IGB are based on this idea of creating intragastric balloons.

The Orbera intragastric balloon, made in 2005, is a single spherical silicone balloon with a diameter of up to 13cm.

The FDA approves it. It is packed in a compressed state and attached to a self-sealing valve visible on X-rays.

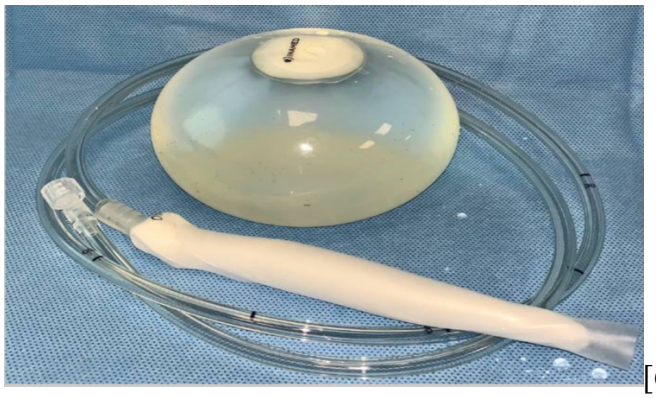
 [60]

Fig 5. Orbera balloon

The balloon is placed via an initial diagnostic endoscopy and is orally inserted into the gastric fundus. A saline solution is filled into the balloon so the balloon can inflate in the gastric fundus. Every step is done under supervision through an endoscope. After the saline solution inflates the balloon, the system closes, creating an immediate vacuum. This results in the valve self-sealing. The tube detaches easily and gets removed orally, leaving the balloon in the stomach.[61] The Orbera balloon can stay in the patient's stomach for up to 6 months. After this period, the risk of complications such as perforation or sudden emptying of the balloon increases. If the balloon perforates or empties, it can deflate and obstruct the bowel. Sedation and endoscopy are necessary for deflation and removing the Orbera intragastric balloon. Also, a forceps and a double-channel endoscope may be required for this procedure.[62] In the last few years, a second generation of the Orbera intragastric balloon has come to the market. It is called Orbera365. This generation of balloons can stay in the patient's stomach for 12 months and has similar characteristics.[63]

Spatz/Spatz3 Balloon

The Spatz3 balloon is a third-generation Spatz intragastric balloon system. Typical for this system is the adjustability in volume. It increases or decreases the balloon's volume during the whole treatment. In classical balloons, this is only possible during the initial inflation.[64] It is one of the first intragastric balloons that can stay in the patient's stomach for up to 360 days. Through that, the patient has more time to change their lifestyle habits, such as changing food or activities. A negative point of the Spatz3 is the outer surface. It isn't an entirely smooth surface, such as many other balloons. The filling valve at the insertion side has a little protrusion, forming a small tail. On the other hand, the little tail can work as a functional advantage. It can prevent the deflated balloon from moving into the patient's duodenum. The Spatz3 has currently been approved by the European Union CE mark.[65]

The Spatz3 intragastric balloon is a round pouch filled with salt water. It has a small filling tube combined with a small special valve. This valve allows for modifying the volume inside the balloon in situ. This balloon can be adjusted in volume to optimise patient comfort and weight loss efficacy. The balloon is divided into three parts. The main parts are the balloon, a silicone anchor, and the silicone filling tube. The silicone anchor is used for balloon insertion and removal. It is also helpful to prevent migration. Through the silicone filling tube, the doctor can modify the balloon's fluid volume and deflate the balloon in the patient's stomach.[66] It is fixed at the endoscope during insertion. The balloon is inflated visually with 400- 700 ml of saline solution. After that, the valve

is secured with a blue nylon loop. While giving pressure on the loop, the valve is positioned in the oropharynx. Finally, the placement is confirmed with an endoscopy. [67]

If the balloon gets deflated or in case of the patient's intolerance, such as vomiting, the balloon can be removed endoscopically using forceps. In this situation, the filling catheter is used.

The filling catheter can reduce the balloon volume by 100-300 ml by aspiration. This exact process is used 3 months after the balloon is implanted. After 3 months, the patient usually stops or minimises weight loss, so the balloon can be readjusted by increasing the volume to 250 ml.

After that the intragastric balloon must be deflated in the reverse way of the inflation. Endoscopic extraction can be more complex because of its morphology and size, and anaesthesia is necessary for this procedure.[68]

ReShape Duo integrated dual balloon system

The ReShape Duo integrated balloon system consists of two silicone poaches. These two silicones poach are filled separately and relate to a short helve. This minimizes the risk of balloon migration in the patient’s intestine if one of the two balloons accidentally deflates. With the flexible structure of the two balloons, it is possible that the balloons can perfectly adapt to the shape of the patient’s stomach. The Reshape Duo balloon system is an approved system which is implanted orally. With an endoscopic guidewire, the duo system is placed into the patient’s abdomen. The balloon is inflated with up to 450 ml of saline fluid, but it is recommended to use a smaller volume. It can occupy up to 900 ml of the patient’s stomach, leaving the gastric anatomy entirely naturally shaped. Anesthesia and an endoscope are required to deflate the balloons after the treatment period of 6 months.[69]

MedSil intragastric balloon.

The MedSil intragastric balloon is filled with a saline solution of a maximal volume of up to 700 ml. Insertion of the MedSil device is quite like other intragastric balloons. The patient can swallow the empty balloon under the supervision of an endoscope. The main difference to other intragastric balloons that can stay in the patient’s stomach is that the MedSil balloon will be lubricated from the outside and inside. With this technique, an easier detachment from the filling tube should be warranted. Usually, the MedSil intragastric balloon will also be implanted under sedation and filled with endoscopy. Following the balloon will be inflated with 500 ml of saline. After that, the patient

usually stays for at least 2 hours for observation. After 6 months of the treatment period, the MedSil balloon will be explanted with forceps under endoscopic vision.[70]

Fig 6. MedSil balloon system. A system of tubes for saline solution in endoscopic treatment of the intragastric balloon MedSil®.[71]

Obalon intragastric balloon

Intragastric balloons can stay shorter in the patient's body and don't need to be implanted with an endoscope. One type is the Obalon intragastric balloon. It is a swallowable intragastric balloon with a small, thin-walled 250ml gas-filled balloon. The Obalon balloon enables gastric volume adjustments by additional balloons as needed. It is made of three balloons with a volume of 750 ml. The balloons get squeezed and folded to fit in a galantine capsule, dissolvable in the stomach. This procedure is not done with endoscopic vision but with the help of fluoroscopic visualisation. Fluoroscopic visualisation is a valuable tool to verify if the capsule entered the patient's stomach. A thin tube is fixed to the balloon over the implantation period, and it exits the mouth of the patient once the balloon is swallowed. The catheter inflates the intragastric balloon with an air mixture of nitrogen. After inflation, the catheter will be detached, and the balloon can freely self-arrange in the patient's body. The balloons can stay inside the patient's stomach for up to 4 months.

An endoscopy is required to remove the Obalon intragastric balloon. Usually, all three balloons will be deflated by and removed endoscopically. All these procedures happen under general anaesthesia. Recently, a new implantation system for the Obalon intragastric balloon was released. It uses magnetic resonance for real-time observation of whether the balloon enters the patient's stomach.

As a result, each patient is less exposed to radiation, making the procedure more patient-friendly and straightforward. Also, the Obalon system is used in paediatrics and is indicated in Europe, even for patients with a lower BMI of 27 kg/m2.[72]

[73]

Fig 7. Swallowable Obalon balloon

7.2 Non-invasive intragastric Balloons (4-month)

Allurion intragastric balloon

The Allurion balloon is an intragastric balloon with a similar shape and function as the popular endoscopically placed intragastric balloon named Orbera. The Allurion intragastric balloon is the only one with its possibilities. It's the only intragastric balloon that doesn't require an endoscope or anaesthesia. Even for removal, no anaesthesia or medical device is necessary. The Allurion intragastric balloon offers people with contraindications for anaesthesia or endoscopic placement an alternative option for general weight loss. On the other hand, eliminating risk factors with pre-implantation endoscopy is impossible.

Potential mucosal lesions like ulcers or anatomical abnormalities like hiatus hernias can lead to unexpected complications while the intragastric balloon is inside the patient's stomach.[74]

The balloon is made of soft parts. Through that, it is foldable and fits into a small capsule that can be swallowed. The capsule, with the balloon inside, is connected to a thin catheter with a total length of 75cm and a diameter of 1.3 mm. This catheter is attached via a self-sealing valve to the balloon. Because of that mechanism, the balloon can unfold in the patient's stomach. The capsule can be swallowed with water like a tablet. If the patient has difficulties swallowing the balloon, the physician can help with a medical guide wire inserted into the catheter to make it easier. With this approach, the physician can insert the capsule into the stomach. After that, the balloon's position will be checked with an X-ray. This is possible because of an X-ray dense marker. After

confirmation of the balloon, the balloon gets inflated with a solution up to 550 ml. The catheter will be explanted after the intragastric balloon is pulled back. These procedures take about 20 minutes and can be done in an outpatient meeting. After 4 -months, the device will empty by itself. The absorbable material in the valve degrades, leading to a deflation of the balloon. The construction of a thin polymer film combined with non-rigid components allows the patient to pass the deflated balloon naturally in the gastrointestinal system. This futuristic system will enable physicians access to intragastric balloon treatments without endoscopic experience.[75]

The easy usage of the Allurion intragastric balloon can also lead to false implantation of the balloon in patients who are unsuitable for intragastric balloon treatment. This can lead to a high risk of intolerance in this patient. Also, the lack of previous endoscopic evaluation can lead to potential stomach pathologies, which could affect the tolerance of the intragastric balloon. The Allurion intragastric balloon is the only one that can be swallowed and naturally passed without endoscopic procedure.

8. ENDOSCOPIC INTRAGASTRIC BALLOONS: CLINICAL OUTCOME

8.1 Effectiveness for body weight loss

The Orbera intragastric balloon is one of the most used intragastric balloons. In 2016, Moura et al. conducted a meta-analysis evaluation of the efficacy of the opera intragastric balloon combined with a dietary intervention compared to a placebo intragastric balloon combined with a diet plan for weight loss management. The analysis combined 9 out of 12 randomised controlled trials published up to 2014. Those results of the randomised controlled trials showed significant positive effects in the group with the Orbera intragastric balloon and the weight loss diet. The Orbera intragastric balloon group, combined with the weight loss diet, achieved more significant reductions in general BMI than the placebo intragastric balloon group combined with the diet plan. The intragastric balloon group generally achieved a BMI reduction of 1.4 kg/m2 and a difference in weight loss of 3.5 kg.

According to the student's t-test, the Orbera intra-gastric balloon group showed an EWL - Excess Weight Loss of 14% compared to the placebo intragastric balloon group. When looking at all data, this data wasn't statistically significant because of the heterogeneity of the studies. One main problem of the study was that the randomised trials RCTs were collected over long periods and operated in the early times of the Orbera intragastric balloon. The second main problem was the small number of patients participating in this study. The persons joining each study group were

between 8 to 31 persons per group. Only in one study did 187 patients and 139 controls participate.[76]

Usually, the Orbera intragastric balloon is filled with a saline solution with 400 to 750 ml volume. To rethink and control the clinical outcomes related to filling volumes, Kumar et al. operated a comprehensive meta-analysis that should show a possible relationship between adverse effects of weight loss and general compatibility of the patient. This major study included 44 smaller studies involving 5500 patients, which makes it one of the most significant meta-analyses that compare clinical results of the Orbera intragastric balloon. The first important result of this study was the non-correlation between filling volumes from 400 to 700 ml to the patient's total body weight loss (TBWL). After six months of treatment, the average total body weight loss was 13.2%, not correlating to the filling volume. This lack of significant difference could be related to the more minor increase in the diameter of the balloon when using the maximum volume of 700ml. The diameter of the balloon when filled with 700 ml is around 11 cm compared to a balloon filled with 400 ml, where the diameter is around 9 cm. Also, no significant associations were found between early removal rates (P – 0.1), reflux symptoms (P – 0.64) and gastric ulcers (P - 0.09).

The study showed a clinical benefit when using a filling volume of 600 to 650 ml per patient. This volume range reduced the incidence of esophagitis by 2.4% to 9.4% if the volume was 600 ml or less (P- 0.001). Also, the general migration rate was 1.7% higher for a balloon with more than 600 ml (P-0.004).[77] Another systemic review managed by Yorke analysed 26 studies involving 6101 patients and published a loss of 15.7 kg and a BMI of 5.9 kg/m2. Nearly all 26 cases were case series and not randomised controlled trials. In this case, 23% of all patients experienced vomiting and nausea. 20% of all patients also experienced mild to severe epigastric pain. The general mortality mainly triggered by gastric perforation was 0.1%.[78]

For several reasons, intragastric balloon meta-analysis faces problems getting enough data from well-controlled randomised controlled trials (RCTs). Usually, only a few reliable randomised controlled trials (RCTs) compare intragastric balloon treatment with placebo intragastric balloons. This lowers the general statistical validity. Another problem is the inconsistent weight loss statistics in all meta-analyses, making it difficult to get precise conclusions. Also, the direct comparison between different intragastric balloons is rare because data for the newer balloon generations is usually missing. Only the Orbera balloon has a long clinical history and is recommended worldwide by most clinicians. That's one of the main reasons many clinicians worldwide are unwilling to change to newer balloons for public research.[79]

One of the most up-to-date studies was published from five Brazilian clinics in 2017. This study included 5874 patients implanted with an intragastric balloon with characteristics of an Orbera balloon. It was filled with 700 ml of solution. After six months, the patients had a general weight loss of 19.2 kilogrammes and a total weight loss of 18.4%. The success rate of this intragastric balloon treatment and a total body weight loss (TBWL) of over 10% was accomplished by more than 85% of all patients. The average BMI decreased from 36.94 to 30.08 following excess weight loss (EWL) of 65.66% - $P < 0.0001$.[80]

Spatz intragastric balloon

Another revolution of intragastric balloon systems was a variable and adjustable intragastric balloon named Spatz. This configuration allows the regulation and adjustment of the volume of the intragastric balloon based on the patient's weight loss. The Spatz intragastric balloon enables the volume to be adjusted after implantation. The Spatz3 intragastric balloon is the third generation of adjustable balloons. Between 2010 and 2014, a comparative study by Russo evaluated two balloon systems. He compared the BioEnterics intragastric balloon and the Spatz intragastric balloon. Thirty patients took part in this study. In 20 patients, the BioEnterics intragastric balloon was implanted. The rest of the patients got the Spatz intragastric balloon. The study's main goal was to compare these two balloons regarding complications, weight loss, and retention of lost weight. The BMI of all patients was between 37 - 46 kg/m2, ranging from 103 to 165 kg. Two patients from each group had intolerance issues, so the balloon was removed early. One additional BioEnterics patient had problems with balloon deflation. Also, in three additional Spatz patients, the volume of the balloons had to be adjusted due to intolerance. With these adjustments, two of the three patients didn't achieve any weight loss.

After the treatment period, the results of both intra-gastric balloons were highly similar. Both patient groups achieved, on average, a weight loss of 20 kg with a reduction in BMI up to 32kg/m2 on average. Six months after the treatment in the BioEnterics patient group, a weight gain average of 6 kg for the 10 patients was achieved. A similar result was gained in the Spatz patient group. It was also an average of 6kg after the 6-month treatment period.[81]

Another study by Abu Davyeh in the USA compared the benefit-risk profile of the Spatz3 intragastric balloon in 187 patients with only lifestyle modifications. He conducted this study over 32 weeks. The treatment group with the implanted Spatz3 intragastric balloon achieved an average total weight loss of 14.9%. Compared to the treatment group, the control group, using only lifestyle modification methods, achieved an average total weight loss of 3.6%. Adjusting the balloon volume

between the 4-8 months, it helped the patient to lose extra 4.7% of weight. In all patients, nearly 40% of the patients were able to hold their weight. In the study, complications also played a crucial role. In nearly 4% of cases, patients had serious complications with gastric ulcers.[82]

Fittipaldi-Fernandez conducted another study. He had a group of 180 patients randomly divided into two groups. The first group got an implantation with the Spatz3 intragastric balloon filled with 600ml of saline solution. This group's volume was fixed to 600ml saline solution over the study period. In the second study group, the volume of the balloon was adjusted to 850 ml of saline solution. After six months, all intragastric balloons were removed. The patient group with the fixed volume of saline solution had a decrease in BMI average from 39.5 to 32.8kg/m2 ($P<0.0001$), a body weight loss from 111.8 to 90.2 kg ($P<0.0001$) and an excess weight loss from 41.5 to 22.9 kg ($P<0.0001$). In the other patient group, a more significant average weight loss of 4 kg was achieved by balloon volume adjustment. This more substantial weight loss led to a higher total or excess weight loss in this group. All studies showed the effectiveness of the Spatz3 balloon, but the complication rate was nearly 16% compared to older balloon systems.[83]

A newer cross-sectional study was published in 2020 by Schwaab et al. with 470 patients who were treated with an Orbera non-adjustable intragastric balloon or an adjustable balloon called Spatz. In 326 patients, the non-adjustable intragastric balloon was implanted. In 144, the adjustable balloon. Of these 470 patients, only 414 finished the whole treatment cycle. The non-adjustable treated patient group managed a total body weight loss of 15.4% the adjustable treated patient group, which achieved an average weight loss of 15.5%. Two hundred sixty-four patients treated with the non-adjustable intragastric balloon, and 93 patients treated with the adjustable intragastric balloon achieved an excess weight loss of over 25% with a statistically significant difference of $P – 0.038$. This study shows that general balloon volume adjustments did not significantly be effective. 67 Spatz intragastric balloon group patients got a volume adjustment during treatment. After this adjustment, this patient group achieved an excess weight loss of over 25% compared to the rest who didn’t get a volume readjustment. It showed no significant difference $P – 0.203$.[84]

All the results show an effective treatment with both intragastric balloon systems loss in overweight patients. The adjustable intragastric balloon did not achieve significant benefits regarding excess weight loss outcomes.

ReShape Duo IGB

In 2013 Ponce et al. managed one of the first studies of the ReShape Duo intragastric balloon. He implanted the intragastric balloon in 21 patients and compared it with nine patients with only diet

management. This was one part of the first phase of the REDUCE study. Eventually, this first phase was stopped because the results didn't seem achievable. Following that, the study was redesigned. After six months, the balloon from the 21 patients was explanted, and the differences in excess weight loss between the two groups were compared. After comparing both groups, no significant differences in excess weight loss were noticed. Those patients who used the ReShape Duo balloon lost twice as much excess weight loss (32%) compared to the food diet (18%). After another six months, 64% of the patients treated with the intragastric balloon maintained their weight.[85]

The results of the REDUCE study were published in 2015, and 187 patients were treated with the ReShape intragastric balloon, and 139 patients were treated with diet treatment. In the intragastric balloon group, the average excess weight loss (EWL) was about 25.1% compared to the diet treatment group, which achieved an average excess weight loss (EWL) of 11.3%. During the study, some complications occurred when using the ReShape intragastric balloon. The balloon deflated in nearly 6% of cases, but no balloon migration occurred.

Nearly 9% of all patients had problems with balloon intolerance. In these cases, the balloon had to be removed early. One of the biggest problems was the development of gastric ulcers in the gastric caesura in nearly 35% of all patients treated with the intragastric balloon. Most of the ulcers result from the pressure applied by the balloon’s tip. After the adjustment of the tip, the rate of gastric ulcers dropped significantly to 10%.[86] The ReShape intragastric balloon is an actual method for weight loss in obese people. According to the ReShape Duo intragastric balloon, with over 202 patients, one of the latest studies was managed in 2018 by Agnihotri et al. In nearly all patients, the balloon was explanted after six months of treatment. The average BMI decreased to 32.8 from 36.8 kg/m2 during this treatment period. Also, a total body weight loss (TBWL) of 11.4% and an excess weight loss (EWL) of 29.9% was achieved. Also, some complications occurred during this treatment time. In 66.4% of all patients, nausea was one of the main complications. In 49%, vomiting and 25.2%, abdominal pain were common side effects. 6.4% of all patients needed early balloon removal because of intolerance. Only in one patient did balloon migration occur, which was removed by operation.[87]

The Obalon intragastric balloon

Sullivan et al. compared the gas-filled intragastric balloon with a lifestyle modification group. This trial contained 387 patients from 15 medical centres in the United States. Of these 387 patients, in 185 patients, the swallowable intragastric balloon named Obalon was implanted. The rest of the patients swallowed a placebo capsule. All the patients were observed over six months. After six months, the total body weight loss was estimated. The Obalon patients achieved an average total

body weight loss (TBWL) of 6.6% versus controls, which got an average total body weight loss (TBWL) of 3.4% - P -0.0354. At 48 weeks, 88% maintained the weight loss, with a total body weight loss (TBWL) of 6.9% after 48 weeks. In the whole clinical trial, only 0.3% got any severe complications besides one patient who got gastric ulcer bleeding. Not many clinical trials were published regarding the Obalon intragastric balloon. That's why most clinical trials contain a small number of patients.[88]

Mion et al. managed a clinical trial with only 17 patients and 43 intragastric balloons. They wanted to evaluate the efficacy of weight loss over about 4 months. On average, all the patients achieved an excess weight loss (EWL) of nearly 36.2%. The patients also reduced their general BMI from 35.3 to 32.2 kg/m2. None of the patients had any problems or complications during this treatment period.[89]

De Peppo et al. managed a clinical trial in 2017 with 17 overweight paediatric and adolescent patients. Over nearly four months of treatment, a significant reduction in average BMI from 35.2 to 32.1 kg/m2 was observed in the study group. Even no significant complications appeared over the treatment time. Comparing these two clinical trials, the general efficacy of the Obalon swallowable intragastric balloon can be highlighted. In both clinical trials, nearly no complications appeared within paediatric, adolescent and adult groups.[90]

The Allurion intragastric balloon

The newest intragastric balloon is called the Allurion intragastric balloon. The Allurion balloon is self-removing after 16 weeks through the patient’s gut. One of the most significant advantages is the placement and removal without endoscopy or anaesthesia.[91]

One of the newest studies managed by Ienca et al. contained 1770 patients using the Allurion intragastric balloon. Because of the self-removal of the intragastric balloon, the trial period persisted for 4 months. After the four months of treatment, the result showed an average weight loss of 13.5 kg, an excess weight loss (EWL) of 67%, a total body weight loss (TBWL) of 14.2%, and an average BMI reduction of 4.9kg/m2. In the clinical trial, no severe complications occurred besides the endoscopic removal of 52 balloons due to patient intolerance. Only 11 balloons were vomited, and only three deflated balloons required surgical removal because of intestinal obstruction.[92]

A microscopic study in Italy with 38 patients was presented by Genco et al. The Allurion balloon was implanted in 38 patients over 4 months. An average weight loss of 12.7 kg and excess weight

loss (EWL) of 26% was achieved. The active treatment group exhibited a 4.2kg/m2 BMI reduction with 11.6% weight loss.[93]

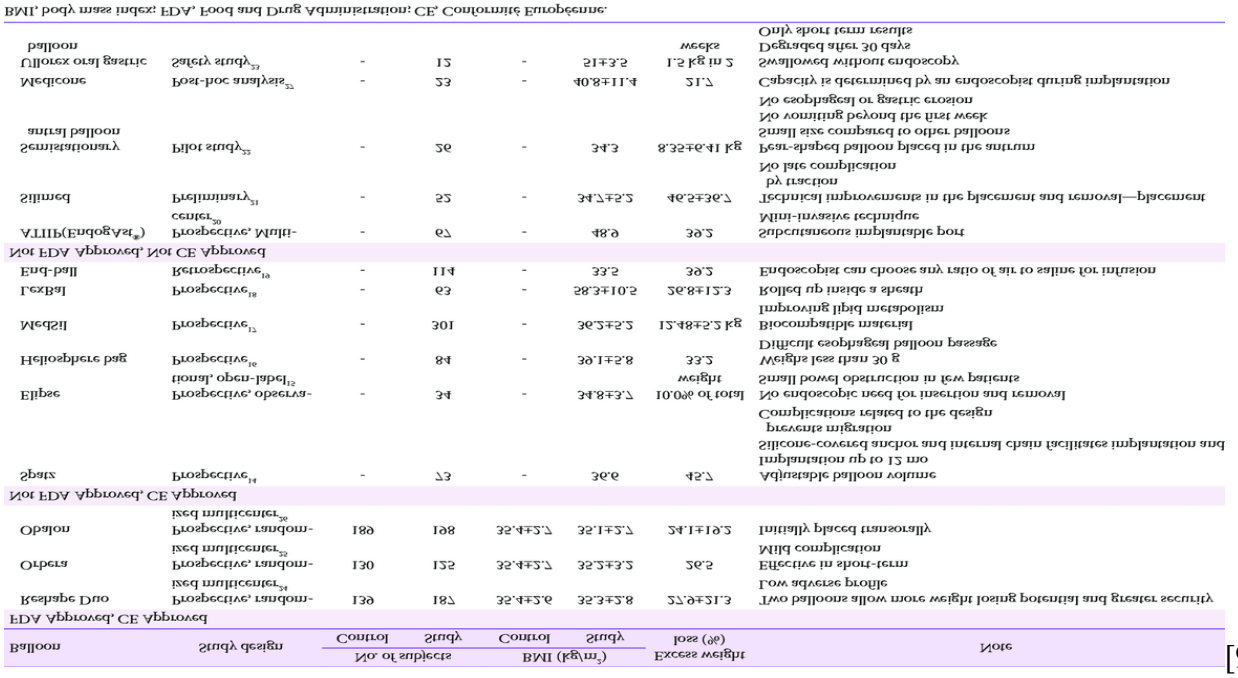
One of the most significant clinical trials was conducted in 2020 by Vantanasiri et al. A meta-analysis of six clinical trials with 2,013 patients treated with the Allurion balloon was published. Also, in this study, the average total body weight loss was determined. After 4- months of treatment, the average total body weight loss was about 12.8%. In this study, 0.2% complained about serious adverse effects. Only three patients experienced a small bowel obstruction because of an early deflated intragastric balloon. Only one patient experienced severe complications like gastric perforation, but it could be resolved surgically. The Allurion intragastric balloon showed some vast advantages in patient handling. No endoscopy is needed for implantation of this intragastric balloon, which results in fewer complications while implanting the balloon.[94]

Also, in 2020, another meta-analysis was published using seven different Allurion intragastric balloon studies by Ramai et al. After four months of treatment, they compared all results and found an average total body weight loss like the other studies. This study's average total body weight loss (TBWL) was 12.2%, with an excess body weight loss (EWL) of 49.1%. In this quite complex study, 37.5% of all patients complained about abdominal pain, 15.4% complained about diarrhoea, 29.6% complained about vomiting and 0.5% about small bowel obstruction.[95]

One of the latest studies was conducted in 2020 with 96 patients with an implanted Allurion intragastric balloon. Also, in this study, they compared the results after four months of implantation and achieved a total body weight loss of 12.1%. The average patient achieved a BMI reduction of 4.9 kg/m2. Even the complication rate was quite like the previous studies, with an average intolerance rate of 3.1%. At one point, 1% of all patients got removed early because the balloon deflated too early. This resulted in the failed discharging of the deflated balloon. During the last week of treatment, close to the balloon self-deflation, 11.5 % of patients experienced diarrhoea and 21.9% suffered from abdominal pain.[96]

One of the latest treatment plans for the Alurion balloon lasts 12 months. This treatment method is called sequential allurion balloon placement. Over 12 months, two allurion balloons are placed, with a two-month break between each balloon treatment. After the first allurion balloon treatment, the average weight loss is -14.7kg. After the first treatment, a two-month break is recommended. During this time, between the 1st and 2nd balloons usually, the patients gain an average weight of 1.4 kg. After this break, the second allurion balloon will be swallowed, and usually, the patients achieve an average weight loss of 8.8 kg after the second balloon. The patients will achieve an

average weight loss of 22 kg using the sequential Allurion balloon placement treatment of 12 months. The average weight loss after the first balloon is 14.4%. After the second balloon, 10%, and after two sequential 22.8%.[97]



BMI, body mass index; EDA, Food and Drug Administration; CE, Conformité Européenne.

Balloon	Study design	No. of subjects: Control	No. of subjects: Study	BMI (kg/m²): Control	BMI (kg/m²): Study	Excess weight loss (%)	Note
Spatz	Prospective[14]	-	57	-	36.6	42.7	Adjustable balloon volume Silicone-covered anchor and internal elastic facilitates implantation and prevents migration Complications related to the design Implantation up to 15 mo
Not EDA Approved, CE Approved							
Obalon	Prospective, randomized multicenter[20]	168	161	32.4±5.7	32.1±5.7	54.1±19.5	Initially placed transorally Mild complication
Orbera	Prospective, randomized multicenter[22]	130	152	32.4±5.7	32.5±3.5	36.2	Effective in short-term Low severe profile
ReShape Duo	Prospective, randomized multicenter[24]	136	187	32.4±5.6	32.3±5.8	57.6±15.3	Two balloons allow more weight losing potential and greater security
EDA Approved, CE Approved							
Allurion oral gastric balloon	Safety study[32]	-	15	-	21±3.2	1.2 kg in 5 weeks	Swallowed without endoscopy Designed after 30 days Only about team results
Medicone	Post-hoc analysis[33]	-	53	-	40.8±11.4	51.7	Capacity is determined by an endoscopist during implantation No esophageal or gastric erosion No vomiting beyond the first week
Semaglutide+ER	Pilot study[35]	-	36	-	34.3	8.35±6.14 kg	Small size compared to other balloons Year-shaped balloon placed in the antrum No late complication by traction
Silimed	Preliminary[21]	-	25	-	34.7±2.5	46.2±36.7	Technical improvements in the placement and removal—placement
ATTiP(EndoGast®)	Prospective, Multi-center[30]	-	63	-	48.9	39.5	Mini-invasive technique Subcutaneous implantable port
Not EDA Approved, Not CE Approved							
End-ball	Retrospective[19]	-	114	-	33.2	39.5	Endoscopist can choose own ratio of fit to deflate for infusion
LexBal	Prospective[18]	-	63	-	28.3±10.2	36.8±15.3	Rolled up inside a sheath Improving lipid metabolism
Medsil	Prospective[17]	-	101	-	36.5±2.5	15.48±2.5 kg	Biocompatible material Difficult esophageal balloon passage
Heliosphere pag	Prospective[16]	-	84	-	36.1±2.8	23.5	Weight loss after 30 g
Elipse	Prospective, operator-friendly, open-label[12]	-	34	-	34.8±3.7	10.0% to total weight	No endoscopic need for insertion and removal Small bowel obstruction in low patients Complications related to the design prevents migration

[98]

Fig 8. Intragastric balloon study Design, Number of Subjects, Weight Loss, Advantage, and Complication

9. COMPARATIVE ANALYSIS OF ENDOSCOPIC AND NON-INVASIVE INTRAGASTRIC BALLOONS

Based on the clinical outcomes and data analysis, a detailed comparison of 6-month endoscopic and 4-month non-invasive intragastric balloons can be provided. This detailed analysis of both types of balloons will focus on their effectiveness, safety profiles, patient tolerance and recommendations for different kinds of patients. By comparing endoscopic and non-invasive intragastric balloons, this comparative analysis should guide which balloons are best for each patient.

9.1 Weight loss efficacy

Over a treatment period of 6- months, all endoscopically placed intragastric balloons, such as the Orbera and ReShape Duo, showed significant weight loss results. In the meta-analysis by Moura et al. from 2016, the Orbera balloon showed an average BMI reduction of 1.4 kg/m2 with an excess

weight loss of 14% compared to a placebo intragastric balloon. The largest cleaning clinical trial, which was 6 months, involved the Orbera intragastric balloon and involved 5874 patients. The Orbera balloon highlighted an average weight loss of 19.2 kg with a total body weight loss of 18.4% over a period of 6 months. Combining these endoscopically placed intra-gastric balloons with dietary modifications can provide effective weight loss management.

The volume-adjustable, endoscopically placed intragastric balloon named Spatz3 also provided significantly effective results over 6 months of treatment. Clinical trials of Russo and Abu Dayyeh showed an average total body weight loss of 14.9% and 20kg. The feature of volume customisation did not significantly show an improvement in excess weight loss compared to non-adjustable intragastric balloons. It shows the limitations of volume customisation in specific patient groups. The ReShape Duo intragastric balloon achieved the highest excess weight loss with an excess weight loss of 25.1%. Nevertheless, endoscopically placed intra-gastric balloons will always be associated with higher and more severe complication rates than non-invasive intra-gastric balloons. One main complication is gastric ulcers, intolerance by the patients and complications during the endoscopy.

Non-invasive intragastric balloons like the Obalon and Allurion balloons usually have a shorter treatment period of up to 4- months. The Obalon intragastric balloon is a swallowable balloon which can be placed without endoscopy. The patient can swallow this balloon on its own under the supervision of a medical physician. The Obalon intragastric balloon achieved an average total body weight loss of 6.6% in a clinical trial by Sullivan et al. in 2016. Compared to the 6-month endoscopically placed intragastric balloons, the Obalon intragastric balloon is less effective in weight loss but shows fewer complications. The Allurion intragastric balloon is self-removing after 4 months and can achieve average total body weight losses of 12.2 to 14.2% with an excess weight loss of 49.1 to 67%. Some studies showed these results. Only 0.2% of all patients experience severe complications and side effects using the Allurion intragastric balloon. Because of its non-invasive, self-using placement and removal, the Allurion balloon nearly reduces all procedural risks.

In general, endoscopic intragastric balloons achieve a more significant weight loss over their treatment period of 6-months. On average, they achieve a total body weight loss (TBWL) of 18 to 25%. Compared to endoscopic balloons, non-invasive intra-gastric balloons only reach an average total body weight loss (TBWL) of 6 to 14% over their 4 – 4-month treatment period. The Allurion intragastric balloon could be an excellent choice for patients seeking a safer treatment method with fewer complications, even if its total body weight loss is less than the endoscopic balloons.

Combined with a shorter treatment period of two months, the non-invasive intragastric balloons could be an excellent choice for patients who also prefer a short treatment period.

9.2 Safety and Tolerability of two intragastric balloons

In the modern world, not every patient is suitable for endoscopic or non-invasive intragastric balloons in the same way. In general, endoscopic intragastric balloons will induce more complications and procedural risk factors in their 6-month treatment period than non-invasive intragastric balloons. Endoscopic intragastric balloons show higher total body weight losses but also higher common complications such as nausea, vomiting and abdominal pain. For example, the ReShape Duo intragastric balloon usually has a higher complication rate than the other balloons, such as a 35% incidence of gastric ulcers and an intolerance rate of 9%. This leads to early removal of the balloon in some patients. Due to intolerance, the in-volume adjustable intragastric balloon, named Spatz, requires volume adjustments in nearly 16% of all cases. Usually, the early removal rate of endoscopic intragastric balloons differs from 6 -16% due to intolerance or complications. Compared to the endoscopic placed intragastric balloons, the non-invasive balloons show significantly better tolerance rates over the 4 - months of treatment. The Allurion intragastric balloon only shows a 0.2% complication rate or severe side effects. A similar outcome is indicated by the Obalon balloon, with a complication rate of 0.3%. The non-invasive placement, without anaesthesia or endoscopy of the intragastric balloon like the Allurion balloon, significantly improves the tolerance rate of the patients. Only 3.1% of Allurion intragastric balloon patients require early removal due to intolerance. For patients who prioritise a safer and non-invasive method, the self-removing function of the Allurion intragastric balloon is a great option. In general, non-invasive intragastric balloons are much better tolerated with lower complication and removal rates than endoscopic implanted intragastric balloons. On the other hand, endoscopic balloons achieve higher weight loss averages combined with higher risk factors, which could be more suitable for patients who prioritise more significant weight loss.

9.3 Clinical Indication and Patient Suitability

In general, the choice between a non-invasive and endoscopic intragastric balloon depends on the needs of the different patients. All individual needs should be considered, such as BMI, the general tolerance of each invasive procedure, and personal weight loss goals. Patients with a BMI of 35kg/m2 who want a great amount of weight loss over a treatment period of 6 months and are willing to undergo anaesthesia and endoscopy are good candidates for endoscopic intragastric

balloons. Also, patients who fail lifestyle modifications and refuse bariatric surgery can think about endoscopic intragastric balloons.

Not invasive intragastric balloons are a better option for patients who want a safer and less complicated way of weight loss. Balloons such as the Obalon or Allurion with a treatment period of 4 – months are a better option for patients with lower BMI - 30-35kg/m2. These balloons are also an option for patients who want a safer and less complicated way of weight loss. These balloons are an ideal option for short-term treatment with a low complication rate. All in all, both intragastric balloons are great options for weight loss in overweight patients. The choice of the intragastric balloon should be considered based on the following factors: BMI, tolerance, and weight loss goals.

10.Conclusion

Intragastric balloons are a very effective and safe method for patients interested in weight loss reduction. It is a minimally invasive intervention, particularly for patients who are not able to undergo bariatric surgery or failed in lifestyle modifications. In this literature review thesis, endoscopic intragastric balloons' general weight loss outcomes (6 months) were compared to those of non-invasive intragastric balloons (4 months). It also compared safety profiles, individual patient compliances, and each intragastric balloon's price range. The thesis results underline the importance of individual balloon selection for each patient by considering weight loss outcomes, safety mechanisms, comfort and efficacy. This thesis provides a more detailed overview of individual balloon selection based on weight loss outcomes of endoscopic (6-month) and non-invasive (4-month) intragastric balloons.

Intragastric balloons showed highly effective weight loss outcomes over each treatment period. Comparing both intragastric balloons, an individual effectiveness is demonstrated. In general, endoscopic intragastric balloons, like the Orbera or Spatz3 balloons, can achieve higher weight loss outcomes with an average total body weight loss (TBWL) of 13 - 18%. Also, their excess body weight loss (EWL) of up to 65% is more significant than the excess weight loss (EWL) in non-invasive intragastric balloons. The highlight of the Spatz3 intragastric balloon is its adjustable volume flexibility, which allows even more substantial weight loss results. Due to their extended treatment periods and possible volume adjustments, these intragastric balloons can restrict the individual patient’s caloric intake.

In general, non-invasive intragastric balloons such as the Allurion or Obalon balloons achieve fewer weight loss outcomes, with an average total body weight loss (TBWL) of up to 14%. Also, their

excess weight loss (EWL) is slightly less than that of endoscopic intragastric balloons. In general, they can achieve 49-65%. The lower volumes and smaller treatment durations of non-invasive intragastric balloons can explain these results.

An advantage of non-invasive balloons is their non-surgical implantation, making them a good option for patients looking for a less invasive procedure. The long-term efficacy of both balloon types highly depends on the patient's lifestyle modifications and motivation for long-term weight loss. On average, the endoscopically placed intragastric balloons show better long-term weight maintenance because of their more extended treatment period. Comparing the safety mechanisms and complication rates of both intragastric balloons, a significant difference can be seen due to the placement and removal methods. While endoscopic intragastric balloons need endoscopy and anaesthesia, non-invasive balloons can be swallowed by the patient. Anaesthesia and endoscopy can increase the risk of aspiration and oesophageal injury. Common side effects of individual anaesthesia can be vomiting, nausea, and general discomfort. In nearly 80% of patients, these complications can appear in the first weeks of treatment. Endoscopic intragastric balloons also have a higher complication rate for gastric ulcers and balloon migration, which can lead to surgery.

The patient can implant non-invasive intragastric balloons, so no anaesthesia or endoscopy is needed. This significantly reduces the risks of complications such as aspiration or oesophageal injuries. Because of the non-invasive implantation procedure, only 20 - 30% of patients are complaining about nausea, vomiting or abdominal pain. Some side effects, such as balloon deflation and migration, appeared at the beginning of the non-invasive intragastric balloon placement. Adjustments could reduce these side effects in modern intragastric balloons. The simplicity of non-invasive intragastric balloons makes them a good choice for patients with higher complication rates. For the working effectiveness of intragastric balloons, the well-being and comfort of the patient regarding the treatment are highly important. No anaesthesia or endoscopy is needed for non-invasive intragastric balloon procedures, which can benefit the patient's overall well-being. Compared to non-invasive intra-gastric balloons, endoscopic placed intragastric balloons require more commitment due to invasive procedures such as anaesthesia or endoscopy. Patients are usually more motivated to undergo this invasive procedure because of its more substantial weight loss outcomes.

The adjustable customisation in volume in some endoscopic intragastric balloons, such as the Spatz 3 balloon, improves the general tolerance rates. Also, the personal needs of volume increase or decrease can be implemented. Also, some financial factors can be a factor in choosing the best intragastric balloon for the patient. The financial ranges between endoscopic and non-invasive intragastric balloons can differ by thousands of euros. The patient must pay for anaesthesia,

endoscopy, and balloon removal when implanting endoscopic intragastric balloons. The cost of this kind of balloon can vary from 3000 to 5000 euros. On the other hand, more effective weight loss outcomes can save money for repeated weight loss procedures after the balloon treatment.

Compared to endoscopic placed intragastric balloons, non-invasive intragastric balloons can be more cost-effective because of the absence of anaesthesia, endoscopy and balloon removal after the treatment period. This makes non-invasive intragastric balloons attractive for people with lower financial budgets while keeping nearly similar weight loss outcomes as endoscopic placed intragastric balloons. Non-invasive balloons like the Allurion and Obalon systems range from 2500 to 4500 euros. On the other hand, because of the shorter treatment period and lower weight loss efficacy, additional financial expenditures and treatment procedures may be necessary after the balloon treatment to maintain weight. The cost-effectiveness of both intragastric balloons' short- and long-term efficacy should be examined.

The comparison of (6-month) endoscopic- and (4-month) non-invasive intragastric balloons shows the advantages and disadvantages of both balloons in categories like weight loss outcomes, safety, complications and contraindications, individual patient compliance and financial cost. Endoscopically placed intragastric balloons showed more significant weight loss outcomes over a treatment period of six months. Still, they also required medical interventions such as anaesthesia and endoscopy for implantation and removal. These balloons also provided higher complication rates, procedural risks and higher costs. Compared to endoscopic intragastric balloons, non-invasive intragastric balloons provided lower weight loss outcomes over their treatment period of 4 months, but with less medical intervention, complication rates, procedural risks and financial cost. Both types of intragastric balloon treatment are effective methods for long-term weight loss, including minimally invasive weight reduction.

Additionally, more research and technological perfection are needed to improve weight loss outcomes, safety mechanisms and general accessibility to intragastric balloon treatment. Simple improvements like material improvement, balloon design and more effective volume adjustments could solve current problems regarding intragastric balloons. Long-term studies, including the durability of weight loss and long-term cost-effectiveness, can optimise the general treatment of overweight with intragastric balloons. By analysing individual patient factors, such as medical indications, specific patient factors, and cost-effectiveness, medical healthcare staff can provide more detailed information and advice about the best individual intragastric balloon treatment. This thesis highlights the balance between achieving the optimal medical outcome while prioritising the individual patient’s needs. By comparing individual weight loss outcomes of endoscopically placed intragastric balloons over a treatment period of 6 months with non-invasive intragastric balloons

over a treatment period of 4 months, this study provides insights into the weight loss efficacy, outcome, safety and individualisation of these medical overweight interventions in different patient populations.

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