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Effects Of Lifestyle Modifications (Diet and Exercise) and Balloon Implantation In an Obese Popullation

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EFFECTS OF LIFESTYLE MODIFICATIONS (DIET AND EXERCISE) AND BALLOON IMPLANTATION IN AN OBESE POPULATION.

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ABSTRACT

The high incidence of obesity contributes to increased risk for chronic diseases and is an economic burden. In those with a BMI of ≥ 40 kg/m^2 (severe obesity), or ≥ 35 kg/m^2 with obesity related chronic diseases, bariatric surgery is the only available treatment that results in significant and sustained weight loss. However, bariatric surgery is expensive and has associated risks. An emerging treatment is the use of intragastric balloon which is becoming popular in America, as it's non-surgical, helps with early satiety and is temporary. It is often used in conjunction with a comprehensive lifestyle modification program. A study to determine the safety and efficacy of the Spatz3 device was conducted at the Center for Clinical and Translational Science, Mayo Clinic in Rochester, Minnesota during 2017-2019. The purpose of this study was to evaluate the safety and effectiveness of the Spatz3 balloon in subjects with BMI between 30 and 40 who had failed to achieve and maintain weight loss with a weight control program. Eligible 288 Subjects were studied in a randomized, controlled, multi-center study. The control group received individualized diet and exercise counseling for 32 weeks. The treatment group received individualized diet and exercise counseling plus the Spatz3 balloon for 32 weeks followed by counseling alone for 23 weeks. This paper offers the RD an insight into the rationale for the emerging non-surgical obesity treatment, history of intra-gastric balloons, evidence of their efficacy, experiences of conducting a study and guidelines for appropriate nutritional care of patients post implantation.

INTRODUCTION

The prevalence of adult obesity in the United States (US) has not met the target set up by Healthy People 2020 to reduce obesity to 30.6% , according to the Centers for Disease Control and Prevention (CDC) summary.[1,2] The CDC uses Body mass index (BMI) as a screening tool for obesity. BMI is calculated for adults by dividing weight in kilograms by the square of height in meters (kg/m^2). The CDC categorizes normal body weight to be a BMI between 18.5 to ≤ 24.9 and overweight between 25 to 29.9. Obesity is defined as BMI of 30 or higher. Obesity is further divided into Class 1 (BMI of 30 to<35), Class 2 (BMI of 35 to <40) and Class 3 (BMI of 40 or higher) obesity, the latter is also referred to as extreme or severe obesity. Based on National Health and Nutrition Examination Survey (NHANES) and CDC data, in 2017-2018 the age-adjusted prevalence of obesity among adults was 42.4%, compared to 30.5% during 1999-2000 through 2017-2018. Among younger adults age 20-39 it was 40.0%, among middle age adults age 40-59 it was 44.8% and among older adults age 60 and over it was 42.8%. It was highest among adults age 40-59. There were no significant differences based on gender. Among ethnic groups it was lowest among non-Hispanic Asian adults (17.4%) in comparison to non-Hispanic white (42.2%), non-Hispanic black (49.6%), and Hispanic (44.8%) adults. Non-Hispanic black adults had the highest prevalence of obesity compared with all other race and Hispanic-origin groups. The age-adjusted prevalence of severe obesity in adults was 9.2% during 1999-2000 compared to 4.7% through 2017-2018. It was higher in women versus men. Overall, from 1999–2000 through 2017–2018, the prevalence of obesity and severe obesity increased, but the observed increase in the prevalence of obesity and severe obesity between 2015–2016 and 2017–2018 was not significant. Socio economic factors play a role in the prevalence of obesity. Men and women with less education had a higher obesity prevalence compared to those with college degrees.[3] This pattern was seen among non –Hispanic white, non-Hispanic black, Hispanic women and non-Hispanic white men. In contrast, in non-Hispanic Black men obesity increase was directly related to the education level. Education level did not factor in obesity prevalence among non-Hispanic Asian women and men and Hispanic men. Middle class income group showed higher prevalence than the lowest and highest groups in non-Hispanic white and Hispanic men. However, obesity prevalence was higher in the highest income group compared to lowest income group among non-Hispanic black men. Highest income group in comparison to the middle and lowest income groups showed lower obesity prevalence among non-Hispanic white, non-Hispanic Asian and Hispanic women. Income did not have an impact on the prevalence of obesity among non-Hispanic black women.

Hruby et al. suggest the 'globesity' epidemic we all live in is due to non-modifiable and modifiable risk factors.[4] The authors stated heredity factors such as genetics and family history are beyond one's control and therefore perhaps may be labelled as non-modifiable risk factors of obesity. They categorized

modifiable risk factors as those which generally can be changed by an individual. These modifiable risk factors include: Individual behaviors such as diet (excess caloric intake, calorie/sugar dense foods, certain diseases such as Cushing's disease, psychological conditions and drugs such as steroids), physical activity/sleep, socioeconomic risk factors such as income and education and environmental risk factors such as the built environment, food deserts, viruses, microbiota, Obesogens and obese social ties. The authors project that if the current trends continue, by 2030 ~38% of the global adult population will be overweight and another 20% will be obese. They predict that in the US over 85% of the adults will be overweight or obese by 2030.

In comparison to the US, Minnesota has reported lower obesity rates except for 2002-2007 when they were very close to the national figures.[5] However, from 2008 to 2017 the rate dropped below the national percentage. From 2000-2007 the rate increased from 17.4%to 26% representing an 8.6% increase. In 2018 the obesity prevalence increased by 1.7 points from 2017 to 30.1% which is close to the national rate of 30.9%. Although the change from 2017-2018 was not statistically significantly, the rate of obesity in Minnesota appears to have increased in the past decade.

Data from the Medical Expenditure Panel Survey (MEPS), which is a comprehensive, nationally representative annual survey of the US civilian noninstitutionalized population reported in the US between 2001 (6.13%) and 2015 (7.19%) there was a 29% increase in national medical expenditures devoted to treatment of obesity related illnesses in adults.[6] For the US as a whole, the average percentage of expenditures devoted to obesity between 2010 and 2015 was 9.21% for private payers including commercial health insurance, 6.86% for Medicare, 8.48% for Medicaid, and 4.74% for out-of-pocket payments by patients. The data for Medicare and Medicaid is of interest because it provides an idea of extent of the possible external obesity related costs that are a burden on the society as a whole. Spieker et al. suggest approximately 8.5% of annual Medicare spending is directed towards obesity-related health costs.[7] In 2013 this cost represented $50 billion of the $585 billion Medicare spending. Since the obese Medicare beneficiaries are also more likely to have chronic medical comorbidities this results in increased treatment costs. The authors predict substantial Medicare costs ranging from $3.4 to $4.7 billion over 10 years for 4% weight reduction among at-risk 60- to 64-year-old adults to Gross savings over 10 years of $7446 to $10,126 per capita with a 10% weight loss would be observed.

Overweight and obesity are associated with increased risk of chronic diseases including type 2 diabetes, hypertension, certain types of cancer, joint problems and gallstones. An Pan et al. reported their findings of the relationship between body weight as a determinant of health-related quality of life (HRQoL) among 2 cohorts of the US women.[8] They followed 52,682 women age 46– 71 years in the Nurses' Health Study

(in 1992–2000) and 52,587 women age 29–46 years in the Nurses' Health Study II (in 1993–2001). Body weight (self-reported) and HRQoL (measured by the Medical Outcomes Study's 36-Item Short Form Health Survey) data was collected every four years. Variables such as baseline age, ethnicity, menopausal status, and changes in comorbidities and lifestyle were factored in. Results indicated that over four years weight gain of 15 lbs. or more was associated with 2.05-point lower (95% confidence interval) physical component scores, whereas weight loss of 15 lbs. or more was associated with 0.89-point higher (95% confidence interval) physical component scores. Inverse relationship was found between weight change and physical dimensions as assessed by the questionnaire that included physical function, role limitations due to physical problems, bodily pain, general health, and vitality. However, small relationship was found between mental dimensions evaluated- social functioning, mental health, and role limitations due to emotional problems. It was concluded that weight gain prevention in general or weight loss in obese or overweight women will help improve HRQoL. Obesity is a risk factor for many chronic diseases and is an economic burden on our society and therefore health professionals should focus on its treatment.

TREATMENT OPTIONS FOR PATIENTS WITH OBESITY

In the US, current treatment options for obesity include weight management programs, pharmaceutical treatments, and bariatric surgeries (gastric bypass, sleeve gastrectomy and gastric banding). Irrespective of which treatment option is used, even small weight loss of 5-10% can improve the health profile by lowering blood pressure, cholesterol levels and blood glucose levels.[9]

Weight loss management programs: Weight loss management programs are those which include some combination of dietary change, behavior modification and/or increased physical activity. While most are successful in the short-term, sustaining weight loss requires continual adherence to these lifestyle changes. Greenberg et al. conducted The Dietary Intervention Randomized Controlled Trial, (DIRECT) to evaluate the effects of three diets in a two year study.[10] Three hundred and twenty two moderately obese subjects (mean age 52 yrs., mean body-mass-index (BMI) 31 kg/m2 , 86% men) were randomized to one of the three groups including low-fat, Mediterranean, or low-carbohydrate diets. Results indicated that overall compliance at month 24 was 85%: the highest compliance was in the low-fat group (90%) and the lowest compliance was in the low-carbohydrate (78%) group. Attrition was higher in women and smokers. Factors associated with attrition included higher baseline BMI and less success with weight loss at 6 months. Self-reported adherence to diet was greater on low-carbohydrate diet until month-6, but dropped overall from 81% at month-1 to 57% at month-24. Due to holiday eating significant decrease in diet compliance was reported but the subjects manage to bounce back to some extent. They concluded

that Initial 6-month weight loss of ≥ 5% was the main predictor of long-term success in weight loss and maintenance.

Lenstra et al. conducted a meta-analysis of 27 (20 randomized controlled trials (RCT) and 7 observational studies) studies published between 2004-2015. They quantified adherence to weight loss interventions (education, self-monitoring, group based or individual exercise or diet interventions, peer support, and lifestyle interventions which included both diet and exercise) and identified those factors that promoted long-term adherence.[11] They reported overall diet adherence rates of 60.5% across all of the treatment protocols. Contributing factors for high adherence rates were having a supervised attendance program, social support and diet intervention alone (versus exercise alone). The authors report higher adherence to diet alone versus exercise alone could be attributed to the self-reporting (poor recall/false information) of the diets by the subjects or due to the success with the restrictive diets. Johns et al. conducted a systematic review and meta-analysis of 8 studies and a total of 1022 subjects to compare the weight loss of the combined behavioral weight management programs (BWMPs) that included diet, exercise and a clearly defined behavior strategy with diet and/or physical activity program alone.[12] They included RCT of overweight (BMI ≥ 25) and obese (BMI ≥ 30) subjects or a BMI ≥ 23 in Asian populations age ≥ 18 years and monitored weight for ≥ 12 months from baseline. Studies which used surgery or medications for weight loss or included other lifestyle changes such a smoking and alcohol cessation were excluded. The studies included weekly, monthly or bimonthly one on one counseling/education sessions conducted by qualified professionals. Dietary intervention of the studies selected included low calorie and low fat diets. The authors reported that the combined BWMPs group showed significantly greater weight loss at 3-6 months and 12-18 months. For diet only and combined BWMP weight loss was similar in the short-term but when diet and physical activity were combined weight loss was increased. They concluded that in the short-term and long-term combined BWMP programs are more successful in helping with weight loss than those based on physical activity alone.

Pharmaceutical treatments: According to the National Institutes of Health, National Heart, Lung, and Blood Institute (NIH, NHLBI), the existing pharmaceutical treatments for overweight and obesity work by creating a feeling of less hunger or early fullness and by aiding in decreasing the amount of fat absorbed from the foods consumed.[14] Drugs that work by making one feel less hungry or full sooner include Belvig, Qsymia, Contrave, phentermine, benzphetamine, diethylpropion and phendimetrazine. Orlistat is the drug that reduces the amount of fat absorbed from the eaten food in the gut. Weight loss medications are prescribed in the US for adults with a BMI of 30 or greater (obese) or above 27 with weight related comorbidities such as hypertension or type 2 diabetes.[14] The medications are recommended to be used in conjunction with lifestyle changes that encompass diet, exercise and behavior modification.

The impact of these medications is to provide an additional weight loss of 3-9% of their starting weight compared to lifestyle changes alone. [14] Table 1 gives an overview of the FDA approved weight loss medications.[14]

Table 1: Weight loss medications approved by FDA

FDA approved Weight-loss medications	Approved for	Mechanism of action	Common Side Effects
ORLISTAT (Xenical)	Adults and children ages 12 and older	Reduces the amount of fat the body absorbs from the food eaten	Diarrhea, gas, leakage of oily stools, stomach pain
BELVIG (Lorcaserin) **WITHDRAWN FROM MARKET in February 2020**	Adults	Acts on the serotonin receptors in the brain. Helps feel full after eating smaller amounts of food.	Constipation, cough, dizziness, dry mouth, feeling tired, headaches, nausea
QSYMIA (Phentermine-topiramate)	Adults	A mix of two medications: phentermine, which curbs appetite, and topiramate, which is used to treat seizures/migraines. Curbs appetite and causes early satiety.	Constipation, dizziness, dry mouth, taste changes, especially with carbonated beverages, tingling of your hands and feet, trouble sleeping
CONTRAVE (Naltrexone-bupropion)	Adults	A mix of two medications: naltrexone, which is used to treat alcohol and drug dependence, and bupropion, which is used to treat depression or help people quit smoking. Curbs appetite and causes early satiety.	Constipation, diarrhea, dizziness, dry mouth, headache, increased blood pressure, increased heart rate, insomnia, liver damage, nausea, vomiting
SAXENDA (Liraglutide) Available by injection only	Adults	At a lower dose under a different name, Victoza, FDA-approved to treat type 2 diabetes. Curbs appetite and causes early satiety.	Nausea, diarrhea, constipation, abdominal pain, headache, raised pulse

FDA approved Weight-loss medications	Approved for	Mechanism of action	Common Side Effects
Other medications that curb your desire to eat include • phentermine • benzphetamine • diethylpropion • phendimetrazine	Adults	Increase chemicals in the brain to curb appetite and causes early satiety. **Note:** FDA-approved only for short-term use—up to 12 weeks	Dry mouth, constipation, difficulty sleeping, dizziness, feeling nervous, feeling restless, headache, raised blood pressure, raised pulse

The impact of appetite suppressing medications was reviewed by Shyh et al.[15] They found that Belvig, a serotonin enhancing drug, resulted in a 3-3.7% weight loss over a year of use. They reported headache, fatigue, nausea and dizziness side effects. Qsymia, is a combination of phentermine (appetite suppressant) and Topiramate (seizure medication). Side effects include paresthesia, dry mouth, constipation, dysgeusia, insomnia, dizziness and psychiatric problems and it is not recommended for use during pregnancy.

Kang and Park reported Orlistat, a reversible lipase inhibitor which decreases fat absorption in the intestine, caused a mean weight loss of 2.6 kg at 6 month time point and 2.9 kg at 12 months in obese subjects.[13] Use of this medication is limited by the bothersome gastrointestinal symptoms such as flatulence, diarrhea and liver damage.

The side effects of the pharmaceutical treatments for obesity can be limiting for their long-term use. Due to the lack of long term research trials with these drugs, it is challenging to make a comparison of the benefits of these medications. Medical professionals must take into account the patient's characteristics, metabolic profile, current medications, tolerance for side effects in order to use these effectively.

Bariatric surgery: Fabricatore et al. have suggested for patients with a BMI of 40 or greater (extreme obesity), or above 35 with obesity related chronic diseases (high blood pressure, Type 2 diabetes or severe sleep apnea), surgical intervention (bariatric surgery) is the only available treatment that results in significant and sustained weight loss.[9] According to the authors there is improved morbidity in obese patients treated with a standardized program using a preset selection criterion and multidisciplinary team approach. They also suggest bariatric surgery can potentially result in 25-30% weight reduction and significant improvements in hypertension, asthma, sleep apnea and diabetes. However the downside is surgery can be expensive and has associated risks, including infection, excessive bleeding, adverse reaction to anesthesia blood clots, lung problems, and leakage in the gut. Furthermore after surgery, problems such as bowel obstruction, dumping syndrome, gallstones, hernias, hypoglycemia, stomach

perforation, ulcers, vomiting and malnutrition may occur. The authors stated that the success of the outcome depends on the selection of a suitable procedure and skills of the surgeon.

Roux-en-Y (RYGB) gastric bypass surgery involves creating a small proximal pouch ~30 cc in size from the stomach and connecting it directly to the small intestine. Ingested food goes into this small pouch and then directly into the small intestine. The food bypasses most of the stomach and section of the small intestine. Zingmond et al. reported that within 3-5 years of this surgery, 25% underwent follow-up procedures as a result of infections (8-20% rate).[16] They also mentioned that between 1995-2004, among 60,000 Medicare patients who underwent this procedure there was a fourfold increase in medical expenses (excluding surgery expense) three year post surgery versus three year prior to the procedure.

Sleeve gastrectomy is typically performed laparoscopically and involves removal of 75% of the stomach creating a tube shaped gastric tube or 'sleeve'. The procedure reduces the amount of ghrelin produced by the stomach and decreases the hunger feeling. Serious side effects of this procedure include leakage from the sleeve that can cause infection or abscess, pulmonary embolism or deep vein thrombosis, narrowing of the sleeve and bleeding.[17]

The gastric banding procedure involves creating a small stomach pouch (about 30 cm) by placing a band in the upper part of the stomach. The net effect is to decrease the amount of food that can be consumed at one time. The band can be adjusted to help meet the individual weight goal needs, and can be removed. While less invasive and non-permanent as the other surgical procedures, banding has the disadvantages of displacement or damage of the band and tubing leakage requiring second surgery.[17]

Flum et al. conducted a retrospective study to evaluate the risk of early mortality among Medicare beneficiaries undergoing bariatric surgeries.[18] They included those who submitted claims for the following procedures for treating morbid obesity 1) gastric restrictive procedures without gastric bypass; vertical banding gastroplasty; 2) gastric restrictive procedures without gastric bypass; other than vertical-banded gatroplasty; 3) gastric restrictive procedures with gastric bypass with short limbed (<100cm) RYGB; 4) gastric restrictive procedures with gastric bypass involving small intestine reconstruction to limit absorption. The authors included 16155 Medicare patients that underwent these procedures between 1997 and 2002. Their results showed mortalities of 2% post 30 days and 4.6% post one year. The authors reported among the Medicare beneficiaries the risk of early death after bariatric surgery was considerably higher than previously reported and it was linked with advancing age, male sex and lower volume of surgeries performed by the surgeons.

INTRAGASTIC BALLOON TREATMENT

As described above, bariatric procedures have become popular but are associated with significant morbidity and death, therefore less invasive medical procedures for morbid obesity have been developed. Recently, the FDA approved the Orbera intragastric balloon and the Reshape Duo intragastric balloon for treatment of obesity.[19, 20] Intragastric balloons (IGB) placement is a weight-loss procedure that involves placing a saline filled silicone balloon in the stomach endoscopically. IGB are effective perhaps by one of the three mechanisms: reducing the stomach's volume and thereby resulting in early satiety, changes in gastric emptying and changes in appetite regulating hormones such as ghrelin and leptin.[21] IGB implantation along with a comprehensive lifestyle modification program which includes exercise, diet and behavior modification has resulted in successful weight loss. This weight loss can be maintained with behavior modification.

HISTORY OF IGB

Gleysteen has provided a comprehensive review of IGB treatments. IGB use in the US was first approved by the FDA in 1984.[22] The first balloon was called the Garren-Edwards Gastric Bubble (GEGB) and was designed to be inserted endoscopically. It was a polyurethane cylindrical device filled with 200-220 ml air, with a hollow central channel and a self-sealing valve. The goal was to use this temporary device instead of bariatric surgery and remove it after 4 months. However, slow weight loss and complications were reported resulting in recall from the market in 1992. In 1987 the "Obesity and the Gastric Balloon; A Comprehensive Workshop" was held in Tarpon Springs, Florida. The objective of this workshop was to develop standards for the design of an 'ideal' gastric balloon. It was concluded that an 'ideal' balloon should be made of silicone elastomer, filled with saline, spherical shaped with a smooth surface, have a radiopaque marker, and an adjustable volume between 400-500 ml. IGB use was not recommended for patients who had had prior gastric surgery, and was for temporary use only. Congenital or acquired anomalies of the GI tract such as large hiatal hernia, atresia or stenosis, esophageal and or gastric varices are additional conditions for which the IGB are not recommended.[23] Clinical application of the IGB included safe weight loss prior to surgical intervention and as an option for those who did not qualify for surgical treatment (BMI $\geq$40 or $\geq$35) but would benefit from losing weight and related lower morbidity. Those with BMI above 40 but below 50 and too old for surgery, qualified as well.

After the Tarpon Springs conference, the BioEnterics Intragastric Balloon (BIB) was manufactured by BioEnterics Corporation in 1991 and was used in Europe, South America, the Middle East, and Asia. Later it was manufactured by other countries under the name Orbera Balloon. Endoscopic insertion of BIB has advantages as it is a quick and a safe procedure. Sallet at al reported results of 323 overweight

and obese patients who were treated with BIB along with a lifestyle program.[24] The results at 6 months showed significant reductions in weight (15.2 ± 10.5 kg) and BMI (-5.3 ± 3.4). The authors report at 1-year follow-up, 85 patients had maintained > 90% of their BMI reduction. The side effects included nausea/vomiting (40% of the cases), epigastric pain (20% of the cases) and BIB had to be removed in 11 patients (3.4% of the cases). Minor side effects reported included reflux esophagitis (12% of the cases) and symptomatic gastric stasis (9% of the cases). Balloon impaction was experienced by two patients and spontaneous deflation causing small-bowel obstruction in one patient.

Since the introduction of BIB more companies have developed and used IGB's outside the US. In 2007 ReShape, Duo Integrated Dual Balloon System was manufactured in California but only used in Europe. In 2015 it was approved by FDA for use in the US. This balloon is unique as it is bi-lobed (shape of stomach) and filled with 900mL liquid. The Orbera and Reshape balloons are saline filled and implanted endoscopically in the inflated state. The volume cannot be changed until it is deflated and removed endoscopically. Ponce at al conduced the REDUCE Pivotal Trial, a prospective double-blinded, multicenter RCT of 293 patients over 48 weeks in15 hospitals was conducted to study the safety and efficacy of this balloon and make comparisons of percent excess weight loss (% EWL).[25] The mean BMI of the patients at the start of the study was 35.3 kg/m². It was found that patients in the DUO group (endoscopic balloon implantation plus supervised diet and exercise) experienced weight loss of 27.9 % EWL $\pm$ 21.3 % EWL compared with 12.3 $\pm$ 22.1% EWL in the DIET group (sham endoscopy plus diet and exercise). In the REDUCE trial both the groups were studied for 24 weeks followed by balloon extraction from the DUO patients. The DIET group was given the option to have the balloon inserted at this point and then both groups were studied for another 24 weeks with continued counseling. Throughout the duration of 48 weeks improvements of co-morbidities and quality of life were recorded. Side effects of the balloon were experienced briefly for a week post implantation but were manageable. The balloon was removed prematurely in 24 patients but incidents of death, intestinal obstruction, gastric perforation or balloon migration were not found. Side effects such as gastric ulceration in 35% of the cases and balloon deflation in 6% were reported in this trial.

The Heliosphere BAG designed by Helioscopie Medical Implants Company in France, has been the longest (since 2004) non-US manufactured device in use. This device weighs 30 g and differs from the design developed at the Tarpon Springs conference as it is filled with air and not saline. It is called a bag because it is made out of an internal polyurethane envelope filled with air and the outside is a silicon pouch. Mion at el studied 32 patients with mean BMI of 35 to evaluate the tolerance and weight loss using this air filled balloon.[26] In this study the balloon was inserted under general anesthesia and then inflated with 800 ml air. From the authors findings significant weight loss was reported at 1, 2 and 4

months. At 1 month it was 6 kg followed by 7 and 10 kg at months 2 and 4. They removed the balloon after 4 months but monitored the patients up to a year. In 3 patients they had to remove the balloon prematurely. The authors reported at 12 months- mean weight loss of 7kg and 9 out of the 26 remaining patients had > 10% weight loss: satisfaction with the procedure was 87%. They concluded that the air-filled IGB was safe and its effect on weight loss was comparable to other balloons. Compared to the silicon balloons this bag showed fewer side effects such as nausea, vomiting and discomfort. There were, however, reports of difficulties in retrieving the bag during extraction at 6 months in several patients requiring surgical removal. In 8% of the patients spontaneous deflation and movement of the bag to the intestinal tract before 6 months occurred.

Another design for an air balloon called the Intragastric Prosthesis Endogast was developed in France by Districlass Medical SA. This oval shaped balloon made out of polyurethane had an attached 15 cm long polyutherane catheter which extended through the gastric and abdominal wall into a subcutaneous pocket which was surgically made near the costal margin. The end of the catheter had a stainless steel chamber with self-sealing rubber membrane to allow external injection of air. The purpose of this design was to allow outside control of air volume in the balloon – a starting capacity of 300 mL of air was used. The advantages of this design are that it could be planted for a longer time (more than a year) in comparison to floating balloons however, it has been associated with risk of infection. Gaggiotti et al. conducted a multicenter prospective clinical survey to evaluate the effect of Adjustable Totally Implantable Intragastric Prosthesis (ATIIP) – Endogast for treating morbid obesity study.[27] Fifty seven morbidly obese subjects (mean BMI of 49) showed weight loss of 12.2 kg after a year of insertion. Subcutaneous infection rate was 12%. One patient had complications with local infection and therefore the prosthesis was removed. This design may be helpful in preparing patients for a later bariatric surgery. From the authors findings they concluded that ATIIP is feasible, reproducible, safe, has low risk of complications and helps with weight loss. They indicate the use of this device for the morbidly obese patients > 60 years old and the super obese (BMI> 50).

Two other systems, the Semi-stationary Antral Balloon (SAB) and Silimed Gastric Balloon (SGB) were unique designs developed in Brazil in 2006. These are made of silicon and filled with saline with added contrast medium and methylene blue. SAB has a unique pear-shape at the distal end, is placed in the stomach antrum and attached distally to a 30 cm long silicone duodenal stem with a metallic tip. The purpose of this device is to promote satiety by intermittently blocking the pylorus, delaying gastric emptying and activating stomach and small intestinal receptors. The SGB balloon is circular in shape.

EFFECTIVENESS OF IGB

Courcoulas et al. conducted a 12 month multicenter, prospective, randomized, open label clinical trial of 255 adults.[28] Subjects had a BMI of 30-40, history of obesity for at least 2 years and poor success with traditional weight loss programs such as supervised diet, exercise and behavior modification programs. The study was conducted under the Food and Drug Administration (FDA) Investigational Device Exemption protocol and the goal was to research the safety and effectiveness of the IGB for weight loss in the US adults. Subjects were randomized to the intervention group (endoscopic placement of IGB and lifestyle modifications) or the control group (lifestyle modifications alone).The lifestyle modification program included a low calorie diet of 1000-1500 calories, food and exercise diary, and recommended exercise and behavioral changes. The modification program was implemented for 12 months in the control group; after 6 months, the intervention group had the balloon removed but continued lifestyle changes for another 6 months. The study involved 21 visits for screening and follow-up over the 12-months. At 6 months, weight loss (of total body weight) was -3.3% (-3.2 kg) versus -10.2% (-9.9 kg); at 9 months -3.4% (-3.2 kg) versus –9.1% (8.8 kg); and at 12 months -3.1% (2.9 kg) versus -7.6% (-7.4 kg) in the control versus the intervention group, respectively. At 9 months mean percent loss of weight in excess of the ideal body weight (IBW) was 9.7% and 26.5% in the control and intervention group, respectively. IBW is defined as the weight that is believed to be optimum for a person.[29] In the treatment group 45.6% of the subjects showed at least 15% loss of weight in excess of IBW which was greater than the control group. The balloon implantation group reported symptoms of nausea, vomiting, and abdominal pain. Of these patients, 18.8% had their device removed prematurely due to these side effects or personal choice. In 3.1% of the subjects at the time of balloon removal some stomach changes (infection, outlet obstruction, perforation, and gastritis) were noticed. Based on the results the authors concluded that complementary treatment with the IGB produces modest, short-term (3 and 6 months post balloon extraction) weight loss which is greater than lifestyle modifications alone.

SPATZ BALLOON

Spatz balloons are approved for use in Europe and are widely used for obesity reduction. In the US they are currently under clinical trials investigation by FDA. This balloon is an improvement over the previous balloons as it can be implanted for a longer time period, about one year, the volume can be adjusted to match the desired weight change and it does not move post implantation.[30] A unique feature of this balloon is the extractable thin filling catheter which makes it possible to adjust volume externally to suit the individualized needs of weight loss and tolerability. The Spatz3 device is the only IGB that meets all

the standards defined at the Tarpon Springs conference. This balloon has a smooth surface, is filled with saline, has an adjustable size and radio-opaque markers.

A study to determine the safety and efficacy of the Spatz3 device was conducted at the Center for Clinical and Translational Science (CCaTS), Mayo Clinic in Rochester, Minnesota during 2017-2019. As a registered dietitian in this unit, I was involved in the development and implementation of the study. After presenting the study design I will discuss my role in developing and execution of the comprehensive individualized lifestyle modification program for this study.

STUDY TITLE

A randomized, controlled, multicenter study comparing the Spatz3 Adjustable Balloon System plus diet and exercise to diet and exercise alone

HYPOTHESIS

Patients who receive the Spatz3 balloon for 8 months will lose significantly more weight than those treated with diet and exercise alone.

FUNDING

Funding source is commercial/industry entity - Spatz FGIA, Inc.

OVERSIGHT

The study conducted at CCaTS research unit was approved and manage by the Mayo Clinic Institutional Review Board (IRB) and followed all clinical trial safety and privacy regulations. Prior to being enrolled in the clinical study the subjects were informed of the nature, scope and possible consequences of the study, in an understandable manner, as per IRB guidelines. The original signed consent form was kept by the investigator and a copy was given to the subject. The subjects were free to withdraw from the study at any point. The Iowa State University IRB was not required to approve this study as determined by their assessment form. The study had been completed and closed for enrollment prior to submission of this Creative Component, and no part of the study was conducted by ISU faculty or students after the initial IRB review.

DESIGN

The purpose of this study was to evaluate the safety and effectiveness of the Spatz3 balloon in subjects with BMI between 30 and 40 who had failed to achieve and maintain weight loss with a weight control program. Subjects were studied in a randomized, controlled, multi-center study. The control group received individualized diet and exercise counseling for 32 weeks. The treatment group received

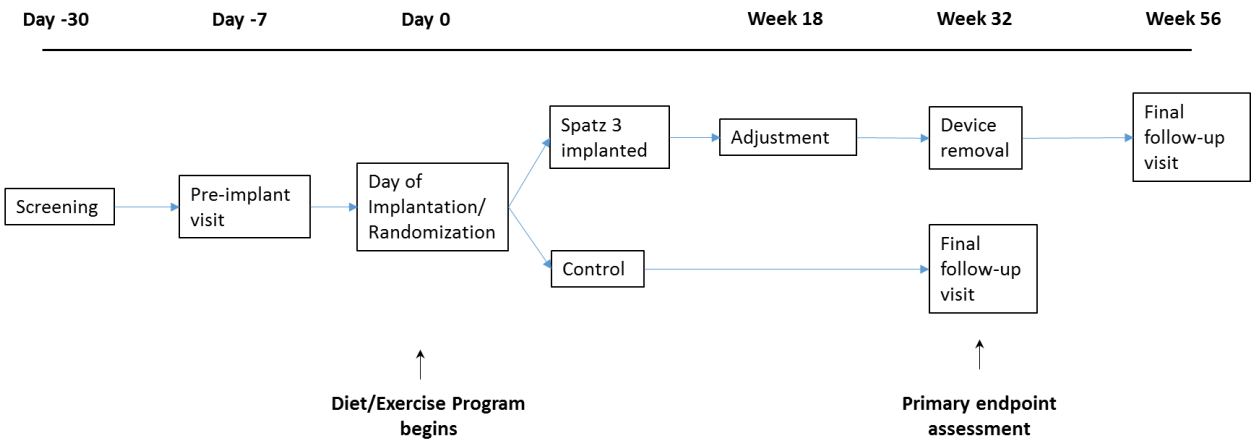
individualized diet and exercise counseling plus the Spatz3 balloon for 32 weeks followed by counseling alone for 23 weeks. 282 eligible subjects were randomized to treatment (188) or control (94) arm. All treatment group subjects underwent endoscopy and only those without endoscopy contraindications had Spatz3 balloon implanted for 32 weeks. Subjects in both groups followed a 1000-1200 kcal/day weight loss diet during the study. The personnel weighing the subjects were blinded to the group randomization. At 18 ± 4 weeks, treatment arm subjects were evaluated, and those that met the criteria underwent an adjustment procedure to increase the balloon volume to achieve extra weight loss. The local physician was approved to make an adjustment to the balloon volume at any time if the patient had symptoms of continued nausea, vomiting, uncontrolled gastro-esophageal reflux or abdominal pain in spite of conservative symptomatic treatment. Volume adjustment guidelines are outlined in table 2.

Table 2: Volume Adjustment Guidelines

For intolerance that continued more than 7-10 days beyond the first 5 days after implantation or that occurred at any time during the 8 months, the investigator may decide to:
● Remove 150 ml from balloon (when initial volume is 450-550ml)
● Remove 100 ml from balloon (when initial volume is 400ml)
● <u>The final volume could not be reduced below 300ml</u>. If medications and balloon volume *down* adjustment did not alleviate the intolerance, the balloon had to be extracted.

At the end of the 32-week treatment period the control group completed the study and the treatment group underwent balloon removal followed by a 24-week follow up. The balloon implantation and adjustment procedures were done endoscopically under sedation. Figure 1 below gives an overview of the study progression. The focus in this Creative Component is the nutritional aspects of the study.

Figure 1. Overview of the study timeline



SETTING

It was a multicenter trial with potentially 10 centers - Mayo Clinic, Rochester; Endoscopic Micro Surgery, Maryland; Surgical Associates of Louisiana, Metairie; Ohio State University Medical Center; Columbus; University of Chicago Med Center, Chicago; NY VA Medical Center, NY; Brigham & Women's Hospital, Boston. Enrollment at each site was limited to 65 subjects. Study inclusion and exclusion criteria are outlined in Table 3 below.

Table 3: Study inclusion and exclusion criteria

INCLUSION CRITERIA
• Age 22-65. • BMI ≥ 30 and <40. • Willingness to comply with the substantial lifelong dietary restrictions required by the procedure. • Obesity (BMI ≥ 30) or at least 2 years. • Failure with non-surgical weight loss methods. • Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing laboratory tests, completing diet counseling. • Residing within a reasonable distance from the investigator's office and able to travel to the investigator to complete all routine follow-up visits. • Ability to give informed consent. • Adequate birth control methods by women of childbearing potential (i.e., not post-menopausal or surgically sterilized). Acceptable birth control methods are limited to hormonal contraceptives (oral, flexible vaginal ring, skin patch, injection), diaphragms, IUDs, condoms with or without spermicide, and voluntary abstinence. Should a treatment arm subject become pregnant during the implantation period, the balloon will be extracted during the second trimester-the timing of which will be determined via consultation with the subject's obstetrician.

EXCLUSION CRITERIA

- Gastrointestinal surgeries with sequelae, bariatric surgery, surgery involving esophagus, stomach, hiatal hernia.
- Inflammatory disease or bleeding condition of the gastrointestinal tract (GIT).
- Gastric mass.
- Hiatal Hernia >2cm or severe intractable gastro-esophageal reflux symptoms.
- Structural abnormality of the esophagus or pharynx that may pose difficulty and risk with passage or removal of the balloon.
- Severe coagulopathy.
- Insulin dependent diabetes or requiring insulin treatment in the following 12 months.
- Health conditions that increase risk of endoscopy.
- Chronic abdominal pain and motility disorders of GIT.
- Hepatic insufficiency or cirrhosis, H. Pylori and cardiopulmonary diseases.
- Serious or uncontrolled psychiatric illness or disorder.
- Alcoholism or drug addiction.
- Unwillingness to participate in an established medically supervised diet and behavior modification program, with routine medical follow-up.
- Medication use: aspirin, anti-inflammatory agents, anticoagulants, gastric irritants, those that affect serotonin levels, anti-seizure and antiarrhythmic medications, corticosteroids, immunosuppressant, diet pills and narcotics.
- Unwillingness to take proton pump inhibitor medication for the duration of the implant.
- Allergies to materials contained in the balloon system.
- Pregnancy or breastfeeding.
- Prior use of intra-gastric devices or prior weight loss programs that could affect weight loss in the past 6 months.
- Symptomatic congestive heart failure, cardiac arrhythmias or unstable coronary disease.
- Respiratory disease such as chronic obstructive pulmonary disease (COPD), pneumonia or cancer.
- Autoimmune connective tissue disorder e.g. lupus, erythematous, scleroderma) or immunocompromised.
- Life expectancy less than 1 year or severe medical condition as decided by the investigator due to increased risk profile.
- Genetic or hormonal cause for obesity such as hypothyroidism or Prader-Willi Syndrome.
- Eating disorders: night eating disorder (NES), bulimia, binge eating disorder, or compulsive eating.
- Endocrine disorders affecting weight.

COMPREHENSIVE INDIVIDUALIZED LIFESTYLE MODIFICATION PROGRAM FOR THE STUDY

TRAINING OF THE REGISTERED DIETITIANS

The funding company conducted a site visit in July of 2016 during which they educated me and my colleague, also a registered dietitian, regarding the balloon environment, purpose of the FDA pivotal trial, role of dietitian, subject selection and symptom management and understanding of the balloon. The training was very important because this was the first balloon study to be conducted at our research unit. The company conducted 2-3 conference calls in fall of 2016 to reiterate the important points, evaluate the understanding of the initial education conducted at the site visit and to address concerns. Dietitian Intake Form (table 5) for screening, dietitian form for weekly and monthly visits (Appendix A) and the physical activity questionnaire (Appendix B) were finalized. Handouts used for nutrition and exercise education (Appendix C) were standardized by the company. All these forms were monitored and audited by the company.

The educational slides used by the company are confidential and therefore they cannot be shared. Following is an outline of the diet.

THE MULTI-LEVEL DIET

The subjects were educated on a four level diet progression as outlined below in Table 4. This diet progression represents the average pace of advancement of diet.

Table 4. Multi level diet post balloon implantation

Stage	Duration	Details
1-Clear liquid	24 hours post procedure	Water, tea, clear juices, Jell-O, broth
2- Liquids	Days 2-4 (May last 7 days)	Dairy products: Cottage cheese, yogurt, pudding, milk, etc.
3- Soft foods	Days 5-10 (May last 15 days)	Tuna, soft boiled egg, cooked chicken/fish, cooked and peeled vegetables, mashed potatoes, etc.
4- Normal diet	After 10-14 days	Foods in accordance with the recommendations for the general population

STAGE 1-Clear Liquids. Day 1

1. Begin drinking water and clear liquids as quickly as possible to avoid dehydration.

2. Drinking should advance gradually with small sips of water with a teaspoon progressing to 1/4thcup water and then half glass of water every hour.
3. Liquids should be spread evenly throughout the day.

STAGE 2- Liquid diet. Day 2-4

1. Advance only if there is good tolerance and no feeling of nausea or vomiting.
2. Gradually start tasting the following: natural yogurt 3% with no added fruit or sugar, soft white cheese, cottage cheese, milk, etc.
3. Patients should drink at least 1 liter of liquids (preferably water) at this stage.
    a. Temporary constipation is very common during the first week after the procedure.
        i. Rationale includes consumption of less food, fiber and liquid intake accompanied by lack of physical activity.
    b. On day 4 patients should add on a daily chewable multivitamin and Probiotic.

STAGE 3- Soft Foods. Day 5-10

1. Patients should only proceed if Stage 2 is well tolerated.
2. Gradually add foods with soft and easily mashed texture.
3. Cottage cheese, tahini, avocado, semolina or corn flour (milk or water base).
4. White bread without crust can be introduced into the diet.
5. Protein should be the main macronutrient at this stage to help replenish muscle breakdown.
6. Protein dishes such as soft boiled egg, tuna, cooked chicken and fish should be emphasized.
7. Protein powders should be added if protein intake is low.
8. Cooked and peeled fruits and vegetables such as apples, pears, zucchini, carrots, squash and sweet potatoes should be added carefully.
9. Drinking 1.-2 L of water throughout the day is important.
10. Continue with Probiotic and Multivitamin.

STAGE 4: A gradual return to a normal diet. Days 10-14.

1. Patients should only proceed if stage 3 is well tolerated.
2. Gradually reintroduce lean beef, chicken, turkey, boiled rice, whole wheat bread and rye.
3. Fresh fruits and vegetables can be gradually introduced at this stage.
4. Drinking 1.5-2 liters of water throughout the day is encourage.
5. Continue with Probiotic and multivitamin.

Protein Intake:

- 0.8 gm. /kg body weight protein is recommended.
- There may be new intolerances to meat.
- Protein powder may be used.

Supplements:

- Start multivitamin and Probiotics on day 4.
- Use Ensure and other supplemental protein drinks if diet is inadequate.

Common Side Effects right after Balloon Insertion:

- Side effects start 0-6 hrs. post implant.
- Last for the first 3-4 days.
- May be challenging to get enough fluids the first 1-2 days.
- Make patients aware that side effects such as nausea, vomiting, abdominal pain/spasms, heartburn, fatigue and weakness are expected in spite of the medications given to relieve them. These usually subside within 3-4 days.

Other Side Effects:

- These may appear days/weeks after procedure.
- Burping/Belching
    - Gastric discomfort triggers frequent saliva swallowing with air.
    - Gastric odor may be a problem.
- Bloating
    - Gas builds up in the stomach and intestines.
- Flatulence
    - Gas builds up in the colon due to fermentation of undigested food.

GENERAL GUIDELINES FOR THE SUBJECT FOR THE FIRST 2-3 WEEKS.

- Eat slowly and with little distractions such as television and smartphone as much as possible.
- Develop a routine for eating meals.
- Eat a variety of foods to minimize dietary deficiencies.
- Introduce foods slowly and by trial and error learn about their tolerance. Tolerance to foods may change after balloon implantation.
- Plan ahead for events such as eating out in restaurants and on special occasions.
- Limit intake of refined sugars and unhealthy fats.
- Moderate exercise including walking 150-200 minutes per week may be started.
- Suitable resistance training is highly recommended to preserve muscle mass during weight loss.

SET-UP OF THE STUDY FOR THE RESEARCH UNIT

Each new study is set up in the *CRU (Clinical Research Unit) Tools* (software program developed by our information technology team) by the multidisciplinary team consisting of nurses, dietitians, pharmacy, lab and the study team study coordinator/investigator. This study set-up and scheduling system is very unique. The set up includes adding a template for the visits (screen, week 1 visit, week 2 visit, monthly follow up) with the dietitian, nurse and/or the study coordinator; verification of consent form; details of the activities to be covered; order in which they meet with the subject; anthropometrics and tests conducted; documents to be used etc. After this the study is activated and ready for enrollment. The visits are scheduled in the system using a code for example 'screen' to facilitate the schedulers to add a patient for the screen visit at our unit. Automatically this subject's screen visit is added on our nutrition calendar. This process gives us an opportunity to prepare our nutrition guidelines for the study and sign off in the system when we are ready for the study. For this specific study it was important that my colleague and I had a good grasp of the study which we did after the training sessions with the company. We both were in agreement with the counselling strategies and we drafted a curriculum of the nutrition topic for follow-up visits. After the study was active revised the template of the visits as needed. The history of the study including the protocol, consent form, study staff, budget, education materials, approvals, modifications and incident reporting may be found in *CRU Tools*.

ONE-ON-ONE VISIT WITH THE SUBJECTS

SCREENING VISIT

Our first visit with the subjects was at the screening visit (> 30 days prior to implantation) and it included physical exam, labs, vitals, consent form signature, psychological evaluation and dietitian visit. We met with the subjects for an hour long appointment during which we collected information for the Dietitian Intake Form. The details of the information collected for this form are outlined in the table 5 below. The objective of this form was to learn about the subject as a whole-their environment, support system, past

efforts at weight loss, personal goals, hurdles and their habitual food intake. It gave an insight into their current weight, readiness to make changes, short term goal weight, calorie and protein needs etc.

Table 5 : Dietitian Intake Form

- Do you Smoke?
- Do you use Oral contraceptives?
- Do you add Nutritional additives to foods?
- Do you have any life stressors
- Do you take laxatives?
- Do you take enemas?
- Do you take diuretics?
- Do you have vomiting episodes more than once a year?
- Do you have a Physical Exercise Routine? Is it less than or more than once a week?
- Any Past Weight Loss Attempts? Were they self-imposed or via a commercial diet center?
- What was your lowest weight since adulthood? How long were you able to maintain it?
- What was your highest weight since adulthood?
- Were you ever underweight as an adult?
- Do you ever binge eat?
- Do you feel that you do not have control over your eating?
- Have you ever self-induced vomiting?
- Have you ever fasted in order to lose weight?
- Have you used enemas, laxatives, diuretics or diet pills in order to lose weight?
- Describe any other difficulties you may have other than weight issues?
- Have you been under psychiatric or psychological care with respect to your weight issue?
- What help do you want to receive with this therapy and counseling?
- What has to happen in order for this therapy to succeed in yielding weight loss?
- Is there anything else that you think is important for us to know about you which hasn't been covered in this questionnaire?
- Share your current diet for a typical day starting with the first thing you eat or drink.
- Please indicate if the following are part of your current diet (Yes/No).
    - Vegetables
    - Fruits
    - Grains/Legumes
    - Milk/milk Products
    - Meat/Chicken/Fish
    - Sweets
    - Water, tea and coffee
    - Sweet/diet drinks
    - Alcohol

Measurements and Nutritional Assessments

	Actual	Ideal
Weight		
BMI		
Height		N/A
Excess Weight		N/A

Nutritional Requirements

Calories: Calculate weight loss calories by incorporating ~500-1200 Kcals/day deficit.
Basal_____ Kcals + Activity = _____ Total Kcals -_____ deficit =_____weight loss kcals/day. NOTE IF DIFFERENT _____

- Protein Needs: ____ kg weight (current wt.) X 0.8 kg=_____ gm/day

Expectations

- Short-term Goals:
- Goal Weight :

Also, we educated subjects on diet and exercise to follow during the study. The control group followed the diet and exercise progression to mimic the treatment group. Diet started on the day of randomization or post procedure depending on the group. Exercise started on week 3. The subjects were encourage to avoid planning too many activities for the first few days after the procedure due to the possibility of low energy level. In addition, they were instructed to be prepared with groceries needed for the first few days. Outlined below are the dietary instructions the dietitian gave to the subjects.

DIETARY INSTRUCTIONS

Stage A: Liquid diet 1-7 days after Balloon procedure

Day 1: one glass of water every hour (half to quarter cup at a time). Later in the day add weak tea.

Day 2: You can add broth (chicken cooked with vegetables and oil-filtered) or pure juices (i.e., grape, apple, pear etc.).

Day 3: You can add milk, coffee, fruit and vegetable juices filtered, jelly, liquid yogurts without pieces of fruit. No carbonated beverages.

Important rules for this stage:

- In the first few days, be sure to drink the above recommended liquids at room temperature-not too cold or too hot.

- Do not drink more than a quarter to half cup at a time.
- Make sure to drink slowly and in small sips to avoid swallowing air while drinking (do not drink with straw).
- Do not drink carbonated beverages.
- Make sure to drink 10 cups of fluids throughout the day.
- To get enough calories and protein it's recommended to keep most of the drinking based on dairy products.
- Make sure to add one tablespoon a day of good fats-like olive oil, canola oil, tahini or avocado to provide essential fatty acids and prevent complications.

Please note: From day 4 onwards the dietary advancement depends on each person and may be slower or faster for you than what is presented.

Table 6: Example of daily routine Days 3-7:

08:00: 1C of coffee with ½ C milk, ½ C water	15:00: ½ C yogurt or white cheese
09:00: ½ C of yogurt	16:00: 1 glass water
10:00: clear juice	17:00: Clear juice
11:00: 1 glass water	18:00: 1 C broth with 1t olive oil
12:00: 1C broth (chicken cooked with vegetables and oil, filtered. Add 1t olive oil	19:00: 1 glass water
13:00: 1 glass water	20:00: 3 t cottage cheese
14:00: 1C coffee with ½ C milk	21:00 1 glass water

Stage B: Blender/soft diet days 7-14:

In addition to foods you drank or ate at Stage A, gradually add the following foods in the order they are written:

- Soft white cheese or cottage cheese, tahini or hummus (low fat), avocado (mashed), oatmeal based on rice flour or corn flour.
- Eggs: After 11-12 days, soft or hard-boiled egg mashed in a blender, Moss tuna (tuna in a blender with olive oil, tahini, avocado or light mayonnaise).
- Purees of vegetables and fruits without seeds, cooked and peeled and ground (zucchini, squash, carrot, banana, apple, pear) Peeled tomato, crushed in a blender (or mix with a teaspoon of olive oil – can help with constipation if it is a problem)
- Fish/chicken (no skin)/turkey-After 8-9 days, ground in a blender.

Important rules for this Stage:

1. The progress at this stage should be gradual-a new food every day. If after adding a certain food you do not feel well (pain, bloating, etc.) stop it and try it again after a few more days.
2. It is recommended to start with 2 T of food several times a day and to gradually increase the amount according to your personal feeling.

3. Keep chewing slowly. Each meal should take at least 20-30 minutes.
4. Check how you feel during meal time and stop eating after a few tablespoons according to how you feel.
5. Be sure to drink 8-10 glasses of fluids throughout the day. Helps to prevent constipation.
6. Continue to take on multivitamin daily.
7. It is important to eat a small meal every 2-4 hours. Do not get hungry before meals to avoid eating too fast or too much.
8. Make sure to keep proper eating habits: eating and sitting at the table without doing other activities such as watching television.
9. At this stage it is important to avoid drinking sweetened drinks or high fat foods that can cause obesity or prevent a decrease in weight.
10. It is important to include protein in every meal.

Table 7: Example of daily routine Days 7-14

07:00: 1 C coffee with ½ C milk. No sugar	15:00: ½ C orange juice or grapefruit juice or vegetable juice; 1 glass water.
08:00: Milk based porridge or 2-3 T white cheese with boiled egg and tomato; 1 glass water	17:00: 2 T of tuna or boiled eggs or 2 T of white cheese with added 1 t tahini; 1 glass water or cup of milk based coffee.
10:00 1C yogurt without fruit chunks, fruit puree; 1 glass water	19:30 Dinner: 2 t avocado or yogurt or repeat lunch, 1 glass water or ½ cup juice.
13:00 Lunch: blenderized soup containing 50 grams of cooked chicken/turkey, carrot, pumpkin, zucchini/carrot and potato with 1t oil. We recommend you eat this meal twice a day.	21:00 (night): Yogurt

Stage C-soft diet (not ground) 14-21 days after procedure:

The transition to this phase is only if you manage well with stage B.

Add all foods gradually and carefully in the following order:

1. Meatballs (beef, chicken, turkey or fish) cooked and mashed with a fork; Bolognese; fish that is cooked or baked. Later add soft and well cooked chicken.
2. Cooked noodles; later add well cooked rice.
3. Cooked vegetables that are peeled and then mashed with a fork; fruit that is soft, peeled and without seeds.
4. Bread or toast; unsweetened cereal.
5. Fresh fruits and vegetables that are peeled, without seeds, and chopped (i.e., tomato, cucumber, soft peach/peart.
6. It is recommended to add only one food a day.

Important rules for this stage:

1. Continue chewing and eating slowly.
2. Eat calmly and orderly. Do not get nervous or too hungry before meals.
3. Each meal should be eaten in stages: First drinking, then eating raw or fresh vegetables, eating protein and finally eating carbohydrates.
4. It is recommended to continue eating small volumes of food to avoid feeling pressure and nausea. If you experience these feelings, it is important to reduce the size of the meal.
5. Allow 3-4 hours between meals.
6. Keep on drinking 8-10 glasses of water throughout the day.
7. Continue to take one multivitamin a day.

Table 8: Example of daily routine-day 14-21

07:00: 1C coffee with ½ C milk, sugar free	16:30 Snack: Fresh fruit or yogurt or slice of bread with 1T white cheese/tahini/hummus. Drink 1 glass water or 1C coffee with milk.
08:00 Breakfast: 1 glass water; 1-2 vegetable with tuna/egg, 1 slice bread, 1 spoon avocado /tahini.	19:30 Dinner Sugar free drinks; 1-2 fresh vegetables, 2T cottage cheese/1 slice of yellow cheese/2T tuna, 2-3 crackers/slice of bread.
10:00 snack: 1C yogurt without fruit; 1 glass water	21:00 Night: Yogurt and 2T Cornflakes.
13:30 Lunch: Sugar free drinks, 2T cooked vegetable or vegetable soup or fresh vegetables; 1-2 meatballs chicken, fish, meat (choose one-not fried); 2T rice/noodles/mashed potatoes/small potato(choose one)	

3-4 weeks after the procedure:

1. You can gradually return to normal eating with good chewing and eating slowly in small amounts at a time.
2. At this time it's important to start gradually exercise-like walking. Maintaining regular physical activity is important from now on will help you to achieve normal weight.
    - It's recommended to exercise 150-200 (2.5-3 hrs.) minutes per week (for example: 34-50 minutes for each workout 3-4 times).

Important rules for the ENTIRE process (in addition to all the rules mentioned so far):

- You should be in follow-up by the dietitian throughout the entire process. The purpose of the follow-up is to support and assist you in solving problems that can occur after the procedure while allowing weight loss at your own rate.
- It is very important to be attentive to your stomach-NOT to your head-and to pay attention to feelings of hunger and satiation. Stop eating when you feel full.

- Planning is the key in the process of weight loss. When you are away from home be sure to take a light meal such as a fruit, sandwich, energy bar, or yogurt.
- Reduce or avoid eating foods that are high in fat, sugar and calories. These will prevent your desired weight (i.e., sweet drinks, milkshakes, ice cream, chocolate cookies, etc.)
- Maintain a balanced and varied diet containing all food groups (vegetables, protein, carbohydrates, fat, vitamins and minerals).
- Protein must be part of every meal.

The subjects were strongly encourage to consider using a food tracker but were not required by the study. The choice of tool (writing, online tracking etc.) for tracking food intake was up to the subject's personal preference. The Dietitian Intake Form, dietary instructions and physical exercise program forms were signed by the subject and the dietitian and sent to the company. At every follow-up visit forms were signed in the same way and sent to the company.

RANDOMIZATION

Subjects were randomly assigned to treatment or control groups with a 2:1 allocation as per computer generated randomization schedule. The statistician created this schedule and it was confidential. At the preimplantation visit the subjects were informed of the randomization. Those randomized to control visited with the dietitian to start their lifestyle modification and those randomized to the treatment group were set up for the procedure.

WEEK 1 AND 2 FOLLOW UP VISITS

Post balloon implantation, week 1 and week 2 follow-up visits were set up to help all the patients get guidance from the dietitian and the study team for symptoms management, diet compliance and address any concerns. The investigator of the study was the surgeon who performed the procedure. She/he tried to meet with the subjects at these visits especially if they were having serious issues including gastrointestinal pain, nausea, acid reflux, inability to drink enough fluids, discomfort in sleeping or other problems. All patients responded differently to balloon implantation so one-on-one counseling was part of the study design.

The Dietitians met with patients individually at Week 1 and Week 2 visits (30 minute appointments) to evaluate the following:

- Weight check: Weight was taken by the nursing staff that was blinded to the group randomization.
- Fluid intake: to ensure ~10 cups fluids daily.
- Food intake: Diet history was taken to check the status of the current diet. The goal was to ensure that they were gradually progressing from liquids to broth, juice, yogurt, milk, cottage cheese during the first week and to soft white cheese, cottage cheese, oatmeal (rice or corn flour), hard boiled eggs, tuna, vegetables/fruits purees without skin and seeds, fish/chicken (no skin) during the second week.
- Protein intake: As expected all subjects added foods to their diet at their own pace and according to their own tolerance. If slow progression to the above stated foods was reported then it was an indication that the protein intake may not be sufficient. Suggestions were given to include protein

supplements such as shakes and powders. We explained the vital role of protein in recovery from the procedure.

- Food tracking: We checked with them to verify if food tracking had been initiated. If so, inquired from them their average daily calories and protein intake. If not, gave encouragement to choose from the written, smart phone or online apps. It was reiterated that research findings have demonstrated more success with initial weight loss and keeping it off if the subjects tracked food intake.
- Diet recommendations: Stage A (day 1-7) and Stage B (day 7-14) diet phases as per diet handout initially used at screen was reviewed again as needed. At screen visit there was information overload for the subjects therefore they welcomed the idea of repeating education in smaller segments.
- Symptoms management: During the first few days the subjects were expected to have symptoms of constipation, stomach pain, nausea, weakness or reflux. We met during week 1 visit to help problem solve. If they were constipated we suggested increasing fluid intake and adding 1 teaspoon of olive oil to foods. For reflux we advised separating out fluids and foods and avoid eating a couple of hours prior to bedtime. Factors responsible for weakness and low energy levels were inadequate diet therefore if tolerated we advised adding ample protein via foods or protein supplements. Consumption of essential fatty acids via foods such as tahini, hummus, avocado etc. helped balance the diet as well. A Multivitamin supplement daily is also beneficial in recovery. Stomachache, bloating or nausea indicated that possibly foods were progressed sooner than the stomach was ready or that the fluids were not spread out. In such a situation we suggested that the diet be stepped backwards until the symptoms are relieved and then adding one new food daily. If the new food caused these symptoms to discontinue it for a few days and tried again a few days later if desired. During week 2 visit the symptoms seemed to decrease in general which is expected. During week 2 stomach ache, bloating and reflux were the most prevalent symptoms. The causative factors for stomach ache and bloating at this stage were most likely due to not eating soft foods, not chewing foods properly, adding many new foods at the same time or eating too much quantity. We recommended that the food be mashed in the blender and starting with only 2 tablespoon of quantity consumed several times a day and gradually increasing the quantity as tolerated. Some patients experienced anxiety at this stage because on one hand they were looking forward to eating more foods but on the other hand they were scared of discomfort and jeopardizing weight loss. We reassured the subjects that following the recommended diet is safe. We reiterated that they would find it beneficial to track their food intake daily as it would give them a clear idea of the calories and protein being consumed.[31] It would help them in planning and tweaking food intake and possibly reduce anxiety. We reminded the subjects that physical activity could be started at week 3.
- Control group: The purpose of meeting with them was to ensure that they were on the same diet as the treatment group. Except for symptom management the visit with these groups was similar. They were asked if they were eating less, slowly and controlling hunger urges. The subjects in this group did not report any issues with following the recommended diet.

The difference between these two visits was the administering of the General Practice Physical Activity Questionnaire at week 2.

MONTHLY VISITS

After the 2 weekly appointments monthly 30-minute follow-up visits were started. Following activities were covered during the appointments:

- Weight check: Weight check by the nursing staff that were blinded to the group randomization.
- Administered company specific follow-up form to collect the following information which was signed by the dietitian and the subject:
    - Is the subject eating less now than prior to beginning the study/balloon implantation?
    - Is the subject eating slower than prior to beginning the study/balloon implantation?
    - Is the subject able to control hunger urges better than prior to beginning the study/balloon implantation?
    - Did the subject fill out a food journal or diary? If yes their average caloric and protein intake.
    - Is the subject having difficulty with the current diet? If yes, explain.
    - Recommendations: Same diet/Change diet? (Circle one). List specific short-term goals?
- Administered General Practice Physical Activity Questionnaire
- We asked open-ended questions e.g., 'share with me one thing that you think went well in the past few weeks' in order to start the session with positivity. Usually they reported a new food they had tried or that they went out to eat and exercised control. We urged them to share more regarding this achievement(s) and how they manage to bring about the change. Some subjects reported that all was going well and there were no problems. For such a situation when they did not open up we asked them to think of one lifestyle thing that they felt they should/could improve. It could have been something as simple as adding one fruit daily or taking the stairs to the third floor office twice a day. In the process of administering the two forms stated above we were able to get a good idea of their problems and deficiencies in food intake and physical activity. In collaboration with the subject we guided them in setting realistic short-term SMART goals aimed at helping with their individual problems and struggles.
- We covered a list of topics with the subjects at the follow-up visits. We let them choose a topic of interest at each visit. Over the holidays the subjects like to get input regarding modifying their favorite family recipes, strategies for eating at the family gatherings and how to disclose to others that were watching their diet. Even if they responded that they already had good nutrition knowledge we attempted to cover a nutrition topic (healthy fats, whole grains, protein supplements, low simple sugars, sodium control, label reading, eating out, holiday cooking) with them to add to their knowledge.

We used copies of the forms, bubble sheets with nutrition topics and our own notes from each visit to help with the follow-ups. For nutrition counseling we were restricted in using education materials to those approved by the company. We referred to MyPlate.com website for covering these topics. This was advantageous because the subjects did not have to deal with paper-work and also they could easily access the website.

CHALLENGES OF CONDUCTING THE STUDY

- Educating both groups on the same diet: The control group had a difficult time following the liquid and the soft diet because they were capable of tolerating regular foods. Although, the subjects had signed a consent form to follow the diet irrespective of the group assignment they questioned it with the investigator. In response to this the study had an IRB modification after which the controls were advised to follow a liquid diet to begin with but then progress to a regular diet. They did not have to follow the diet progressions that the intervention group was supposed to follow.
- Hurdles of compliance:
    - Availability of food: Subjects reported a variety of reasons for limited food choices in their environment including different food preferences from the rest of family members, expense, low usage and wastage of the produce, inadequate choices at work cafeteria and lack of time for shopping.
    - Willingness to try new foods: The treatment group was cautious during progression of the diet to the next level due to the fear of GI side effects and gaining weight. We guided them to add 1-2 new foods daily to help with ease of identifying any problem foods. Food tracking was suggested to get an idea of the caloric intake. In general those who disliked fruits and vegetables tried them for a short period and then went off them. Recipe ideas such as stir fries, salads, pasta replacement, soups, and smoothies were shared with them.
    - Cravings for sweets: Many of the subjects had a 'sweet tooth'. Although post balloon implantation the appetite was decreased they continued to crave sweets at specific times of the day-most commonly afternoon. Strategies suggested included finding a distraction such as walking, reading and alternate food-fruit. Subjects reported finding satisfaction with a mini size candy, Jello, fruit etc. This compliance was followed by a period of week self-control (especially after the treatment group had recuperated) and indulgences with a big bag of candy or missed desserts.
    - Lack of time: In response to our suggestions/ideas 'I don't have the time' was a frequent answer. Finding a balance between work, family life and a healthy lifestyle was a challenge. For physical activity we suggested incorporating daily lifestyle activities such as parking further away, taking stairs, walking breaks at work, family activities-walking, hiking, and biking. One subject came up with a unique idea to use a desk cycle. Some took turns with the spouse to work out at the gym. We suggested online free grocery shopping for those who struggled with time for grocery shopping. Subjects found this beneficial because it had the added advantage of avoiding impulse shopping. Many ideas/resources for helping build simple cooking skills were shared. We reiterated that planning ahead is the key to success. There were good examples of subjects preparing and portioning out main meat/poultry/seafood, vegetable/salad and snacks (nuts, cottage cheese, yogurt, fruit) food items over the weekend. A realistic approach to planning and management of meals and snacks was encourage therefore convenient, prepackage calorie controlled frozen meals for the hectic times were suggested instead of going through the fast food lane. High importance was given to family support and teamwork in working through these issues. Teaming up with significant other/children in meal planning and execution helped as it took some of the burden off the subject and also was instrumental in teaching children healthy eating habits via role-modelling.

- Self-control/Discipline: Compliance to the recommended healthy lifestyle was not consistent. The subjects reported periods of good self-control and compliance followed by (over) indulgence due to burnout and boredom. To overcome the 'all or nothing' phenomenon we suggested that the subjects try taking a day off a week from the diet as long as they mindfully followed the 'hunger signals' and ate when hungry, ate slowly and stopped when felt satisfied. Also, exercising 'one bite rule' was encourage if they badly missed a food. Over the holidays or routinely at work there are many treats in the environment that tested their will power and it was not easy to resist them. There were instances where the extended family members were opposed to the procedure and developed hostile behavior. The family and work gatherings centered around rich and heavy food. We gave suggestions to take foods that they could eat to the pot-luck or/and eat prior to the party.
- Mental health and other health issues: Subjects who had diagnosis of depression and anxiety found it tough to stay driven to eat a healthy well balanced diet and be physically active. We continued to support them and suggested exploring activities and hobbies such as meditation, yoga, knitting, painting, book club etc. that they would find relaxing. We emphasized the important role of stress management. One subject tried basic yoga and found it helpful for relaxing after work. Strenuous physical activity was challenging for those who had joint pains therefore our advice was to try low impact exercises or10-15 minutes of walking 2-3 times daily as tolerated.
- Portion control: The balloon implantation procedure was instrumental in limiting the quantity of food that could be consumed. For the control group it was more challenging. Our recommendations for both the groups were food measuring using a scale and measuring cups/spoons paired with food tracking using an online app or any other mode that worked for the subject. Food measuring may be necessary only for a couple of weeks until one is comfortable 'eyeballing' the foods. After that suggested keeping measuring equipment handy to use when in doubt. Subjects recorded food intake for a few days and then after that due to monotony, time commitment and complexity discontinued it. A few subjects opted to write food and behavior journals and found them helpful in identifying external factors during the day that triggered them to eat snacks. Physical Activity was easier to track for the subjects using smartphones, smart watch and Fit bit.

- Research versus Clinical approach to counseling**:** Generally speaking, during weight loss counseling dietitians do not necessarily bring up the patient's body weight in discussions. An effort is made to direct the conversations towards personalized healthy eating with the goal of weight loss. In research settings the visits are centered around the weight of the patient as per protocol guidelines. We convey to the patient the weight goal of the study upfront. During follow-up visits if there had been weight gain, we started by learning about the reasons and helped set goals in a very diplomatic manner. At the same time it is important for us to build rapport. This can be challenging.
- Lack of psychologist: The study team did not have funding for the psychologist visit. Only one initial visit to evaluate the eligibility for behavior modification was included. We have done studies in the past with psychologist follow-up visits. Patients in those studies found the psychologist's support helpful in providing motivation for behavior modification, identifying obstacles, developing solutions etc. In this study we took on the role of cheerleading.

DISCUSSION AND FUTURE DIRECTION

The study has many strengths as it included a randomized controlled study design. A multidisciplinary approach of a highly trained team including the investigator, study coordinators, RDs, and psychologist to help eligible subjects make individualized lifestyle changes was used. There were frequent one-on-one visits with both the groups to monitor the progress and provide individualized guidance in making changes. If additional care was needed for example if a subject in the intervention group called the study team post-operation to report that they were not keeping fluids down or had a stomach ache, an appointment was scheduled to help solve the problem if the phone call did not resolve the issue. Both the groups had equal numbers of visits and education content. The subjects were not given contact information of the registered dietitians for follow-up questions because this would have been a variable. They were encourage to keep a log of questions and bring them to their next appointment.

The study had limitations. Self-monitoring of food intake and physical activity were optional and self-reported by the subjects. Although the subjects were instructed to follow 1000-1200 calories after they had recovered from the procedure, data was not collected. This was a weakness in the design because tracking food intake from the subject's perspective is a time consuming task and takes a lot of dedication and motivation. Perhaps if it was required for the subjects to mail in food and exercise diaries we would have collected data for nutrient intake as well as diet and physical activity adherence. Group support was missing in this study. Due to patient confidentiality only one-on-one visits could be conducted. The subjects who in the past had tried commercial weight loss programs with group meetings reported that they would have benefited from interfacing with other subjects in this study. It would have given them an opportunity to share and compare their experiences, struggles and problem solving approaches. They asked if they could participate in other commercial programs for group support along with the study but this request was denied. For those who were active on the social media recommendations were made to use blogs selectively to connect with others who had similar weight loss procedures and experiences.

In conclusion IGB is potentially an important tool to help manage obesity and its associated co-morbidities. The adjustable IGB system is safe and effective. Even a small weight loss of 5-10% can improve health profile by lowering blood pressure, cholesterol levels and blood sugar levels. [9] It is a treatment option for those with whom previous interventions have been unsuccessful. Similar positive results were also reported by a retrospective study.[32] In that study, results (demographic, medical and laboratory) from 2 academic centers and 5 private practices were compared for up to a year. The qualifying 202 adults had Reshape IGB inserted for 6 months along with lifestyle modification via diet and exercise for weight loss. At 1, 3, 6, 9 and 12 month time points mean %TBWL was 4.8 ± 2.4%, 8.8 ± 4.3%, 11.4 ± 6.7%, 13.3 ± 7.8%, and 14.7 ± 11.8%, respectively. At 6 months data from 101 patients and

at 12 months data from 12 months was available which revealed that 60.4 % of the patients showed >10% TBWL and 55.4% had >25% EWL. Nausea (73.8% patients), vomiting (49% patients), and abdominal pain (25.2% patients) were the most common side effects reported. One patient needed surgical removal of the balloon as it migrated to the small intestine and resulted in obstruction. It was concluded that the Reshape Duo IGB is a safe and effective endoscopic method for weight loss when used for 6 months.

Studies have also researched implantation of the IGB for a longer duration of time. Brooks et al. conducted a study with 73 consecutive patients at the Nucleus Healthcare Facility in Newport, Wales. In 2011 and 2012 Spatz adjustable balloons were implanted for a year in 73 patients who were > 35 BMI. Mean weight loss of 21.6 kg, 19% weight loss and 45.7% EWL (excess weight loss) was reported from 70 (49 at 12 months, 21 at <12 months) patients who finished the study. Three patients had problems with the catheter as it got stuck in the undiagnosed hiatal hernia or the duodenum and therefore the balloon had to be surgically removed. Failure rate in this study was 4.1%.They concluded that the balloon is an effective intervention for weight loss without the risk of mortality.[30]

As a registered dietitian, my recommendations for future study are to include a combination of one-on-one meetings and group nutrition classes for effective teaching, support groups and promote information sharing amongst the participants. I suggest having the subjects email the food intake online logs or bringing in written diaries for data collection. Similarly recommend giving to the participants a physical activity monitoring device and downloading the data. For both the groups it would have been interesting to have a pre and post randomization/procedure comparison of body composition via a dexa scan. The lifestyle changes and weight loss perhaps may have impacted body composition. However, it goes beyond the scope of a study to research all aspects of the main idea due to limited funding, complexity of the study design and also because the tests conducted should be related to the purpose of the study.

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Appendix A – DIETICIAN: Treatment Arm follow up visits

Date: _____ Subject ID #_____
(Day/Month/Year)

_____
Dietician Signature

Dietician – 1 & 2 week follow-up (after implant)

- Subject Name _____
- Subject Study # _____
- Dietician Name _____
- Weight_____
- Visit Date_____

1. Was the visit done? Yes / No
2. How much fluids are being ingested?

3. Does the subject have sufficient PO intake? Yes / No

Recommend: Same Diet / Change Diet *(circle one)*

Dietician Signature, Date

Dietician – 4 week onwards (monthly visits) follow-up (after implant)

- Subject Name _____
- Subject Study # _____
- Dietician Name _____
- Weight_____
- Visit Date_____

4. Was the visit done? Yes / No

5. Is the subject eating less now than prior to balloon implantation? Yes / No

6. Is the subject eating slower than prior to balloon implantation? Yes / No

1. Is the subject able to control hunger urges better than prior to balloon implantation? Yes / No

2. Did the subject fill out a food journal or diary? Yes / No

3. Is the subject having difficulty with current diet? Yes / No
    a. If Yes, please explain.

Recommend: Same diet / Change diet

Dietician Signature, Date

Appendix B: Physical activity questionnaire

General Practice Physical Activity Questionnaire

Date……

Name……

1. Please tell us the type and amount of physical activity involved in your work.

		Please mark one box only
a	I am not in employment (e.g. retired, retired for health reasons, unemployed, full-time carer etc.)	
b	I spend most of my time at work sitting (such as in an office)	
c	I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g. shop assistant, hairdresser, security guard, childminder, etc.)	
d	My work involves definite physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter, cleaner, hospital nurse, gardener, postal delivery workers etc.)	
e	My work involves vigorous physical activity including handling of very heavy objects (e.g. scaffolder, construction worker, refuse collector, etc.)	

2. During the *last week*, how many hours did you spend on each of the following activities?
Please answer whether you are in employment or not

Please mark one box only on each row

		None	Some but less than 1 hour	1 hour but less than 3 hours	3 hours or more
a	Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout etc.				
b	Cycling, including cycling to work and during leisure time				
c	Walking, including walking to work, shopping, for pleasure etc.				
d	Housework/Childcare				
e	Gardening/DIY				

3. How would you describe your usual walking pace? Please mark one box only.

Slow pace (i.e. less than 3 mph)		Steady average pace	
Brisk pace		Fast pace (i.e. over 4mph)	

Appendix C: Handout for exercise education

Physical Exercise Program for the Spatz3 Adjustable Balloon Trial – for Balloon Patients and Control Patients

Energy balance is the key for losing weight and is an important consideration in planning the proper physical activity.

Research suggests that aerobic exercise of about 1000 kcal per week can result in weight loss of 4-6 lbs. /month. The physical activity should include a balance of resistance training as well as aerobic exercise which should be introduced gradually.

Principles of planning physical activity

- Losing weight is **not** the main goal, it is only a side effect.
- The chosen activity should fit the characteristics of the patient (age, gender ,available time and place ,orthopedic and other health limitations)
- Include exercises that can be done at home on a daily basis with simple equipment (or even with none) or in a gym or club that is nearby and is easy to access.
- Start easy, with appropriate intensity and gradually increase both volume and intensity
- Enjoy the activity – enjoyable activity is easier to maintain
- Make time for the activity on a weekly schedule.

Stage 1-Beginning physical activity (week #3 through 2 months)

The main purpose of that stage is to be active and to raise body awareness

This stage starts for both treatment and control subjects at week #3

Aerobic Exercise

3-4 sessions per week of 15-25 min. of easy to moderate effort (HR=100-120 bpm)

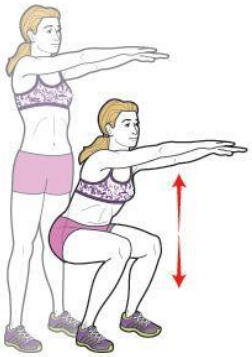
1. Walking outdoors or on treadmill
2. Swimming
3. Riding bicycles (outdoors, indoors, spinning or fitness bike)
4. running

Resistance training and core maintenance

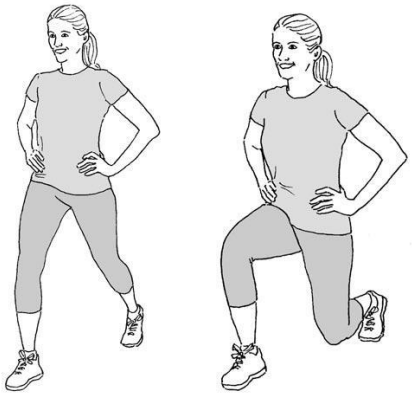
3-4 sessions per week of 15-20 min.1 set of 10-15 repetitions for each exercise.

Lower body (body weight resistance with no extra weight)

1. Half Squats



- Heel raise



- Lunges

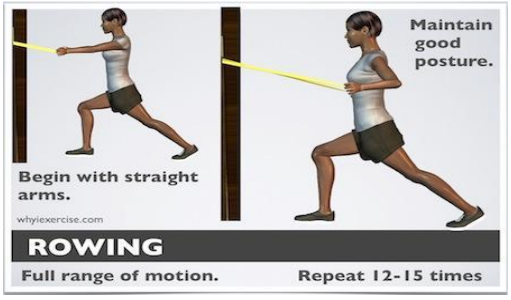
Upper body

Using 3-8 lbs. dumbbells or low resistance rubber band in a standing position

- Biceps curls

- Triceps – elbow extension

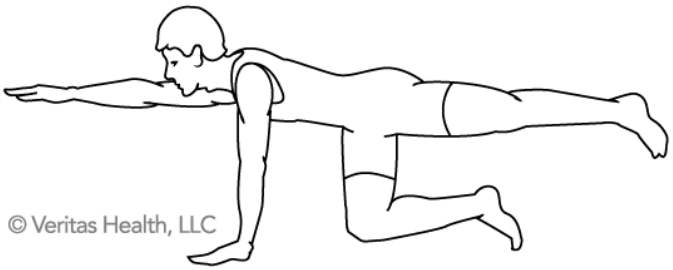
- Rowing



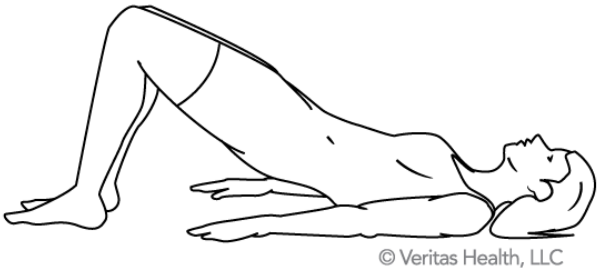
- Pushups in a diagonal position leaning on the wall or high table (low resistance)

- 

Core maintenance

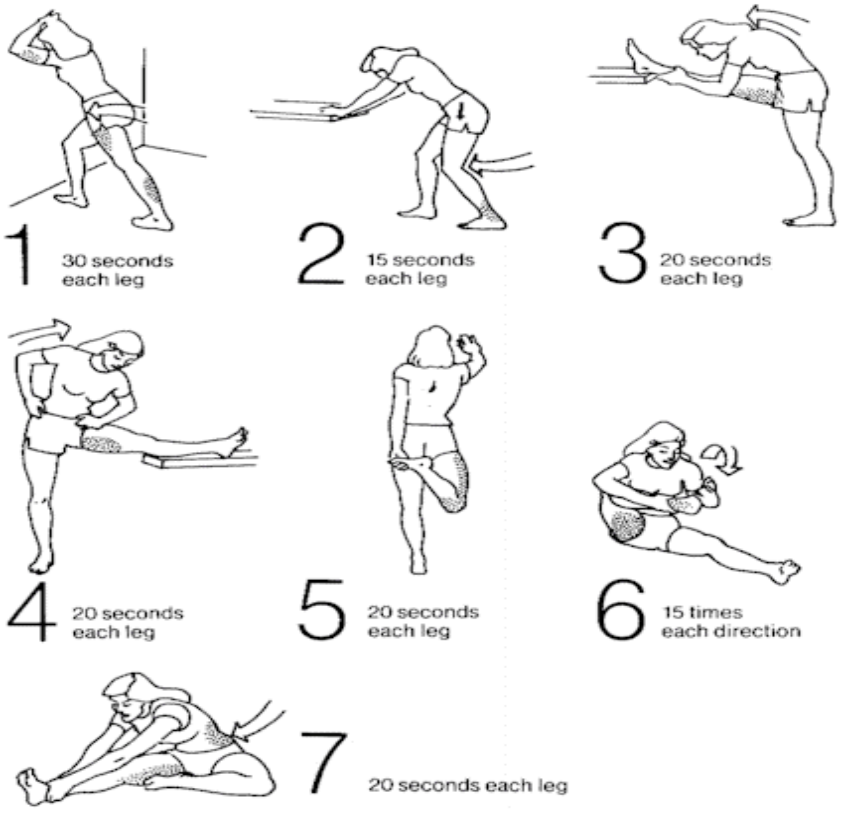


- Quadruped arm/leg diagonal raise
- Gluteal bridge

- 

Stretching

- Hamstrings
- Calves
- Quadriceps



Stage 2- enjoy the effort (months 3-5)

The main purpose of that stage is to find and choose the right activity that suits the patient and try to enjoy more intensive activity

Aerobic Exercise

3-5 sessions per week of 20-35 min. of easy to moderate effort (50% maxHR=120-140 bpm)

Resistance training and core maintenance

3-4 sessions per week of 10-15 min. of 1 set of 12-15 repetitions for each exercise of the exercises shown on the previous stage

Stretching

same routine as above

Stage 3- physical activity as part of daily/weekly routine

(Months 6-8)

Aerobic Exercise

4-6 sessions per week of 25-40 min. of moderate effort (60% maxHR=130-150 bpm)

Resistance training and core maintenance

3-4 sessions per week of 20-25 min. of 1-2 sets of 12-20 repetitions for each exercise of the exercises shown on the previous stage

Stretching

Same routine as above