Effect of Ileocolic-released Conjugated Bile Acid on Satiety, Entero-Endocrine Cell Function, and Body Weight in Patients With Obesity and Abnormal Satiety Phenotype

NCT#05314374

14June2023

EFFECT OF ILEOCOLIC-RELEASE CONJUGATED BILE ACID ON SATIETY, ENTERO-ENDOCRINE CELL FUNCTION, AND BODY WEIGHT IN PATIENTS WITH OBESITY AND ABNORMAL SATIETY PHENOTYPE

Principal Investigator:

- Andres Acosta M.D., Ph.D. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN

Co-Investigator:

- Michael Camilleri, M.D. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN
- Ryan Lennon, M.S., Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN.

Research Fellows:

- Wissam Ghusn M.D. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN
- Sima Fansa, M.D. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN
- Diego Anazco M.D. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN

Key Personnel

- Duane Burton M.A. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN.
- Jessica Stutzman, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN
- Megan Schaefer, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN
- Alison McRae, M.S. Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN

Conflicts of Interest: none

Contents

ABSTRACT:

Introduction:

Obesity is a chronic, heterogeneous complex disease that has reached epidemic proportions. Recently, we identified an abnormal postprandial satiety obesity (APS-OB) phenotype characterized by accelerated gastric emptying, an abnormal postprandial sensation of fullness and reduced satiety hormones such as GLP1 and PYY. In a recent randomized-clinical trial in type 2 Diabetes[1], we showed that ileo-colonic delivery of conjugated bile acids (IC-CBAS) improves glycemia and increases the release of satiety hormones. Elevated fecal Biliary Acids (BA) were also associated to weight loss. However, the specific effect of IC-CBAS in APS-OB is unknown.

Hypothesis:

We hypothesize that IC-CBAS will stimulate enteroendocrine L cell (EEC) secretion of satiety hormones [Glucagon Like peptide 1 (GLP-1), Peptide Tyrosine Tyrosine 3-36 (PYY_{3-36}), fibroblast growth factor 19 (FGF-19), oxyntomodulin (OXM)], in the ileum and colon, inducing weight loss and restoring normal satiety in patients with APS-OB.

Aim:

To study the effect of IC-CBAS on EEC function, satiety hormones, microbiota, and body weight in patients with APS-OB phenotype.

Study design:

This is a single-center, placebo-controlled, double-blinded, parallel-group, randomized 90 days (+/- 5 days) trial to study the effect of IC-CBAS 500 mg and 1000 mg BID on EEC function, satiety perception, body weight and satiety GI hormones, in patients with APS-OB phenotype. A lifestyle intervention will be provided. These consist of an obesity physician consult, a low-calorie diet instructed by a member of the study team, and physical activity and behavioral suggestions. These interventions should last at least the length of the study. In addition, this study will include 2 colonoscopies at the beginning (i.e., before medication/placebo start) and at the end of the study (i.e., after last dose of medication/placebo) in the first 6 patients in each group willing to consent to the colonoscopies (12 patients; 24 colonoscopies in total). Participants will receive a bowel prep (Movi-prep) and follow standard colonoscopy preparation guides. The next day, after an overnight fasting, a colonoscopy with terminal ileum intubation will be performed. The colonoscopy will be done in the GI clinical or research unit and will be supported by sedation based on patients' characteristics (i.e., conscious sedation vs. anesthesia supported sedation). During the procedure, 8 biopsies will be obtained from the ilium, right and left colon. We will include otherwise healthy patients with a BMI > 30 kg/m^2, age range 18-65 years, and APS-OB phenotype. Based on the results of our previous trial comparing weight loss in exenatide therapy vs placebo [2], we calculated a sample size of 18 participants per group (total of 36) with 80% power, 0.05 alpha to detect a 1 kg difference between treatment and placebo groups.

Study Intervention:

Ileocolonic-release conjugated bile acid 500mg tablets will be provided by Bilarm Health Inc., San Diego, CA.

Anticipated Results:

In comparison with placebo, IC-CBAS will result in improved EEC function, increased postprandial incretin secretion, and weight loss when compared to placebo.

Significance:

We expect to demonstrate that delayed IC-CBAS increases satiety, restoring satiety in patients with APS-OB phenotype. This study will provide the basis for future pharmacological studies, exploring the effect of luminal enteroendocrine secretagogues in patients with obesity and APS-OB phenotype.

BACKGROUND:

Overview:

In 2017–2018, 42.4% of the adult population in the US (~88.6 million) were reported to have obesity and, 9.2% had severe obesity (~19.24 million adults). From 1999–2000 through 2017–2018, the prevalence of this disease in adults increased from 30.5% to 42.4%, in the case of severe obesity it increased from 4.7% to 9.2% [3]. The total annual medical costs attributable to obesity were approximately $480 billion[4]. Moreover, obesity related complications include coronary artery disease, type II diabetes, and end-stage renal disease (among others). Severe obesity increases the risk of these complications even further [3], fostering additional expenses and compromising the population's health and quality of life. Obesity and severe obesity have been associated with increased cardiovascular disease mortality. Hazard ratios ranging from 1.29 – 2.21 with a $p<0.001$ were found when cardiovascular disease mortality was compared between subjects with BMI >30 and subjects with normal BMIs (18.5-24.9) [5]. In another study with more than 150,000 postmenopausal US women; the hazard ratio for all-cause mortality in women with obesity and central obesity compared to normal women (adjusted for demographics, socioeconomic status, lifestyle factors and hormone use) was 1.3 (95% CI: 1.27-1.34) [6].

Obesity may be understood simply by balancing energy intake and expenditure. The gut-brain axis plays a significant role in regulating the stages of food intake (i.e., hunger, satiation, and satiety). Gastric sensory and motor functions contribute to energy intake and serve to objectively assess these stages, in particular satiation and satiety [7]. Satiety can be quantifiably measured by visual analog score (VAS) for appetite and gastric emptying of solids. Results of gastric emptying studies can be summarized in half time $T_{1/2}$min [8]. Not only is there a significant correlation between gastric emptying and appetite sensations, but also a correlation with prospective calorie consumption [9, 10]. In deeper analysis of patients with abnormal satiety phenotype, there is a significant lower plasma levels of gastrointestinal satiety hormones (PYY_{3-36} and GLP-1) when compared to normal postprandial satiety participants with obesity. Furthermore, these same group of patients had decreased mRNA expression of PYY in colonic mucosa compared to normal satiety obesity (Calderon et al., Submitted to Cell Reports Medicine).

Current approaches to treat obesity include dietary interventions, pharmacological options, endoscopic devices, and surgery. Despite the advent of obesity therapies, response to treatment still shows high inter-individual variability. Consequently, the segregation and classification of the specific traits that lead to the pathophysiology of obesity are imperative to attempt a guided, efficient, and individualized therapy [8]. In 2015, we showed quantitative characterization of patients with obesity based on gastrointestinal and psychological traits[2]. Furthermore, in proof of concept single-center, randomized, placebo-controlled trials with medication (e.g., phentermine/topiramate, exenatide, liraglutide) and endoscopic procedures (e.g., Intragastric Balloon, endoscopic sleeve gastroplasty) obesity-related phenotypes predicted response to treatment [2, 11-16]. Finally, in a real-world pragmatic trial, the phenotype guided therapy when

compared to non-phenotype-guided resulted in 1.75-fold greater weight loss after 12 months with mean weight loss of 15.9% compared with 9.0% in the non-phenotype-guided group and the proportion of patients who lost >10% at 12 months was 79% in the phenotype-guided group vs. 34% in non-phenotype-guided treatment group [8].

One of the aforementioned food-intake regulating mechanisms is the bile acid pathway. IC-CBAS has been identified in ex vivo models as a secretagogue for EEC, inducing incretin (GLP-1) secretion [1]. Bile acids (BAs) circulate through a complex pathway that regulates their synthesis, secretion, circulation, reabsorption, and excretion. These steroid-derived detergent molecules form micelles facilitating cholesterol absorption through the brush border membrane of the small intestine. The apical Na+-dependent bile salt transporter (ASBT) mediates the active BAs transport in the distal ileum [17]. This process results in 95% reuptake of BAs that enter the small intestine [18, 19]; the vast majority of remaining non-reabsorbed BAs undergo deconjugation and dehydroxylation by colonic bacteria into secondary BAs, prior to excretion in the stools. Passive colonic reabsorption of bile acids recovers some of the 5% remaining bile salts [20]. At this level, reabsorbed BAs act as endogenous ligands for farnesoid X receptors (FXR) and G protein coupled bile acid receptor 5 (GPBAR1 or TGR5) in the enterocyte [18]. These two receptors are stimulated intracellularly, inducing production of fibroblast growth factor 19 (FGF-19) and glucagon-like peptide 1 (GLP- 1), respectively. FGF-19 is a bile acid pathway marker whose primary function is to generate negative feedback into the hepatocytes decreasing the synthesis of BAs[21].

In our previous study, TGR5 was observed in human colonic mucosal biopsies that were also GLP-1 positive [1]. The same study showed increased incretin mRNA expression and GLP-1 release when colonocytes were stimulated ex-vivo with taurocholic acid [1]. There was decreased FGF-19 in patients with obesity and diabetes when compared with controls, as well as when distal EEL were stimulated with conjugated bile acid and compared to placebo [1]. Stimulation of TGR5 results in a rapid increase in incretins, reduced appetite, and improvement in insulin sensitivity [22, 23]. The delivery of bile acids to the distal ileum and colon had positive effects on glucose metabolism in our previous study [1], increased levels of fecal BA were also associated with weight loss in it.

We believe these effects can be seen after metabolic surgery, where bile acid secretion increases significantly after Roux-in-Y gastric bypass surgery. Recent studies showed colonocytes express BA signaling machinery and deficiency of said machinery in patients with obesity and diabetes. In humans, the acute infusion of taurocholic bile acid enemas per rectum or via nasojejunal feeding resulted in rapid increase in GI satiety hormones and increased satiety [24, 25]. Bile acids need to be delivered to the distal ileum and colon to stimulate only distal L-cells and avoid proximal lipid absorption. Thus, it is critical to know, whether the delivery of IC-CBAS will restore the normal satiety in patients with ASP-OB. We hypothesize that the IC-CBAS delivery will stimulate EEC secretion in the distal jejunum, ileum, and colon, thereby increasing the secretion of GLP-1 and PYY_{3-36}. This will possibly restore satiety and induce weight loss in APS-OB phenotype subjects.

The overall research goal is to study the effect of delayed-release IC-CBAS on satiety and body weight in APS-OB phenotype patients when comparing it to placebo. The current proposal is a proof of concept, single center, placebo-controlled, randomized clinical trial in otherwise healthy patients with obesity and abnormal satiety.

Preliminary Data:

Chenodeoxycholic acid delayed release: Initially, we completed a feasibility, 4-day, placebo control trial to test the effect of ileo-colonic delivery chenodeoxycholic (IC-CDCA) bile acid 500 and 1000 mg PO daily in 20 per group healthy volunteers. IC-CDCA produces weight loss in healthy subjects (fig 1). Posteriorly, we completed a 28 day, randomized, double-blinded, placebo-control trial to study the effect of IC-CDCA acid in glycemia in patients with obesity and type 2 diabetes[1].

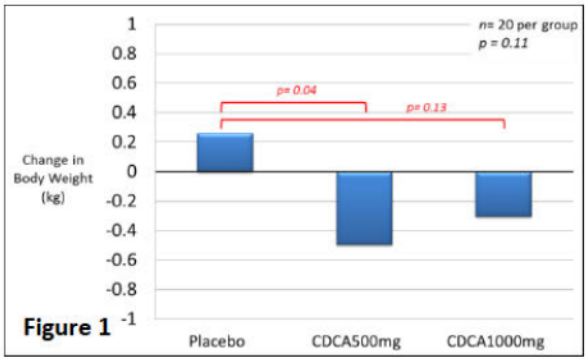


Figure 1

Hypothesis:

IC-CBAS will stimulate EEC secretion in the ileum and colon, increasing the secretion of GLP-1 and PYY_{3-36}, FGF-19, oxyntomodulin (OXM), and restore normal satiety in patients with APS-OB.

RESEARCH PLAN:

Design:

We propose a single center, placebo-controlled, randomized double blinded 90 (+/- 5) day trial, to study the effect of IC-CBAS delivery (500 mg BID for the first week and 1000 mg BID for the rest of the study) on colonic EEC function, postprandial incretins (GLP-1, PYY_{3-36}, FGF-19, and OXM), body weight, and satiety (evaluated with gastric emptying and appetite based VAS) in patients with obesity and abnormal satiety. We plan to randomize 18 participants per group. Participants will complete the following visits: 1) Screening and Consent (virtual); 2) Baseline phenotype, lifestyle intervention, 3) Colonoscopy and Randomization visit prior to medication start (in first 6 patients in each arm) who are willing to consent to colonoscopy), 4) Two (in person or virtual) Study Team visits at 30 & 60 days post randomization,5) Colonoscopy visit and 6) Exit Phenotype visit after taking last medication dose (in first 6 patients in each arm). During the phenotype visits, participants will be phenotyped by measuring energy expenditure, satiety with gastric emptying of solids and VAS scores, satiation with calories consume to fullness, and emotional eating by questionnaires[8]. Resting energy expenditure will be measured by indirect calorimetry, gastric emptying will be assessed with scintigraphy and calories to fullness will be tested in *ad libitum* meal. In addition, participants will have a body composition with a DEXA scan. Blood will be collected every 30 minutes for 6 hours and selected plasma gastrointestinal hormones will be measured. A sample will be stored for venous blood DNA analysis. Stool samples will be collected for 24 hours for microbiome, bile acids and short chain fatty acids. Participants will keep a food, medication, and activity diary. Participants

will receive a bowel prep (Movi-prep) and follow standard colonoscopy preparation guides. The next day, after an overnight fasting, a colonoscopy with terminal ileum intubation will be performed. The colonoscopy will be done in the GI clinical or research unit and will be supported by sedation based on patients' characteristics (i.e., conscious sedation vs. anesthesia supported sedation). During the procedure, 8 biopsies will be obtained from the ilium, right and left colon. During the Study Team visits, patients will meet with the study team to review medication compliance, assess adverse events, and perform a medication dispensation.

The clinical research team will perform a medical record review to acquire possible candidates for recruitment. The randomization scheme will be provided by the study biostatistician. Allocation will be concealed. Pharmacy will provide the medication or placebo. Randomization will be stratified in sex-specific tertiles (low, medium, high) defined by gastric emptying (T1/2, min).

Participants:

Subjects with obesity and abnormal satiety phenotype will be recruited by direct contact from an established database of patients or by public advertisement, including social media. All subjects will be given a verbal explanation of the study, provided time to read and study the written consent form and its information, and given opportunities to ask questions and copy the consent form. Participants will be informed of their right to withdraw from the study at any time without prejudice to their clinical management now or in the future. Consent will be sought by one of the medical doctor investigators or study coordinators, and consent will be documented by the participant's signature on the consent form virtually or in person. All recruitment or contact information will be approved by Mayo's Institutional Review Board.

Inclusion criteria:

I. **Patients with obesity BMI> 30 kg/m^2 and hungry gut phenotype.**
II. Age: 18-65 years.
III. Gender: men or women. Women of childbearing potential will have a negative pregnancy test before initiation of medication and within 48 hours of receiving radioisotope for the gastric emptying study.
IV. Otherwise healthy individuals or with controlled chronic medical conditions such as type 2 diabetes.

Exclusion criteria:

I. Structural or metabolic diseases/conditions that affect the gastrointestinal system, or functional gastrointestinal disorders. For screening the bowel disease questionnaire will be used to exclude subjects with irritable bowel syndrome.

II. Subjects with stool type Bristol classification 6-7 per bowel disease questionnaire.

III. Female subjects who are pregnant or breast-feeding.

IV. Use of anti-obesity medications upon screening (ie., orlistat, phentermine-topiramate, liraglutide, semaglutide, bupropion-naltrexone), metformin or GLP-1 analogs.

V. Individuals who are currently on treatment for unstable cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, endocrine, and psychiatric disease.

VI. Any acute or chronic condition or other disease that, in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in this clinical study.

VII. Significant untreated psychiatric dysfunction based upon screening. Hospital Anxiety and Depression Inventory (HAD) score >11 on depression scale, a self-administered alcoholism screening test (AUDIT-C) score >4 in men or >3 in women, and difficulties with substance or eating disorders determined by the Questionnaire on Eating and Weight Patterns (binge eating disorders and bulimia); will mean the participant will be excluded and given a referral letter to his/her primary care doctor for further appraisal and follow-up. The provider will review the patient's alcohol intake over the past few months to confirm accuracy and determine study eligibility.

VII. Principal Investigator discretion.

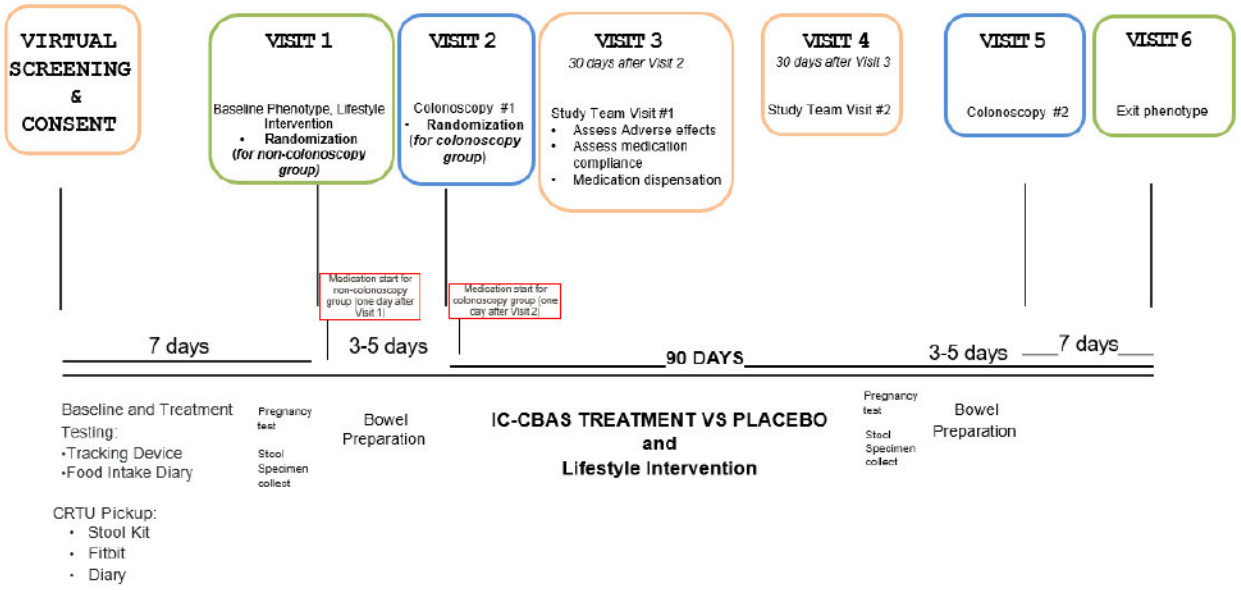
Intervention:

CBAS 500 mg tablets will be supplied by Bilarm Health Inc.. Subjects will take medication or placebo orally twice daily on an empty stomach, 30 minutes prior to breakfast and evening dinner for 90 +/- 5 days. Patients on the medication will receive 500 mg twice daily during their first week and 1000 mg twice daily for the rest of the study.

Methods:

Participants will keep food, appetite, and activity diaries for one week prior to baseline test day[11]. On randomization day they will also receive the randomized medication (delayed release IC-CBAS or placebo). A full medical history and physical exam will be performed and recorded, and a low-calorie diet will be suggested during this visit.

On Day 90 (+/- 5 days), subjects will repeat obesity phenotyping protocol at the exit visit [11] as described previously but will receive the study medication/placebo 30 minutes prior to the test meal.



**Visit 1, 3, 4 and 6 can be conducted at the Clinical Research and Trials Unit (CRTU)in the [redacted] at Mayo Clinic in Rochester, MN.*

Visit 2 and 5 can be conducted at the CRTU or on [redacted]

Screening and Consent (virtual):

During the screening and consent visit, informed consent will be requested either in person or virtually through the e-consent process. We will request medical history, or perform a brief chart review if available, acquire most recent anthropometric parameters, (height, weight, and waist circumference) and we will request completion of questionnaires (Appendix A). The questionnaires will be administered via Redcap and will need to be filled after consenting to determine eligibility. Food and activity diaries will be given to the participants for filling during the following 7 days (baseline and treatment phase). An activity tracking device will also be given to be used throughout the complete study. A stool collection kit be provided to complete 48 hours prior to visit 1.

See appendix A: Questionnaires

Screening & phenotyping questionnaires:

1. GI Screening Bowel Disease Questionnaire
2. Hospital Anxiety and Depression Inventory
3. Bristol stool scale
4. Physical Activity Questionnaire
5. Eating Patterns Questionnaire
6. Body Self Relations Questionnaire

7. Audit C Questionnaire
8. Weight Management Questionnaire
9. Obesity Questionnaire
10. Exercise Regulations (BREQ-3) Questionnaire(survey)
11. Barriers to Being Active Questionnaire(survey)
12. Weight Efficacy Questionnaire(survey)
13. Three Factor Eating (TFEQ-R21) Questionnaire(survey)
14. Physical Exam and History Documentation

Baseline phenotype:

Subjects will collect a random stool specimen 48 hours before visit 1. All the participants will be given an activity tracking device. This device needs to be picked up in the CRTU, alongside with the instructions on how to install it with its corresponding tracking app. They will be required to use this device during the time they are participating in the study. Physical activity data, caloric consumption and medication use will be entered by the participants via weekly diaries, as well as extracting physical activity data from each participant's tracking device account. A food diary will also be given to all participants to fill in the week prior during this week. All questionnaires will be sent and filled during this 7-day period in case they didn't complete them during the screening and consent.

- <u>Visit 1:</u> Baseline phenotype

Participants will attend Mayo Clinic Clinical Research Trial Unit (CRTU) at [redacted] Rochester MN after an 8-hour fasting period.

- They will undergo anthropometric measurements:
  Height, weight, blood pressure, heart and respiratory rates, waist and hip ratio, waist circumference, and temperature.
  Baseline and follow-up characteristics studies:
- Methods of <u>metabolic studies:</u>
  - Body composition will be measured by DEXA (dual energy x-ray absorptiometry).
  - Resting energy expenditure was assessed by indirect calorimetry with a ventilated hood (Parvo Medics, Sandy, UT).

- Gastric emptying (GE) of solids by scintigraphy [9] [8, 11]Images will be acquired at 0, 30, 60, 90, 120 and 240 minutes following the normal clinical gastric emptying testing protocol without a push meal.
- Satiation will be measured by *ad-libitum* meal to measure total caloric intake and macronutrient distribution in the chosen food. Satiation will be reported in calories consumed at fullness (satiation) [8] [11].
- Appetite sensations by visual analog score fasting and every 30 minutes after the standard meal for GE and the Satiation test up to 2 hours [8, 11].
- Blood samples: The fasting blood samples will be collected during the gastric emptying meal and stored at -70° C freezer. We will analyze plasma glucose, insulin, C-peptide, GLP-1, PYY_{3-36}, OXM, FGF-19, 7-α-C4, Adiponectin, Leptin, CCK, Pancreatic Polypeptide (PP), serum bile acids, short chain fatty acids, amino acids[2, 8]. Samples collection, handling, and storage: Samples will be collected after an overnight fast (of at least 8 hours) in the morning. Plasma will be preserved following standard guidelines and protein degradation inhibitors, kallikrein and DPP-IV inhibitors will be added to preserve the samples. Samples will be stored at -80ºC in the PI's laboratory. Plasma hormones and proteomics by radioimmunoassay and/or mass spectrometry measured fasting, postprandial, and every 30 minutes for 6 hours. The primary endpoint being the peak postprandial level (test should be done simultaneously to GE).
- Blood DNA for genome wide association studies (GWAS). These samples will be stored for future research.
- Stool samples: One random stool will be collected at baseline and after treatment for fecal bile acids, short chains fatty acids and microbiome.
- Participants with childbearing potential will undergo a pregnancy test.
- Self-administered questionnaires assessing affect, physical activity levels, attitudes, body image, diet, and eating behavior; details of each questionnaire are provided below.
    - Hospital Anxiety and Depression Scale: HADS will be used to screen for severe anxiety or depression.
    - AUDIT-C Alcoholism Screening Test [26] - The AUDIT-C is a 3-item alcohol screening questionnaire that reliably identifies participants who are hazardous alcohol drinkers or have active alcohol use disorders. This score will be used in screening by the study physician/nurse coordinator. The AUDIT-C is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices. Points allotted are: a=0 points; b=1 point; c=2 points; d=3 points; e=4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive (same as above).
    - Eating Disorders Questionnaire - The Questionnaire on Eating and Weight Patterns-Revised [27], is a valid measure of screening for eating disorders which has been used in several national multi-site field trials. Respondents are classified as binge eating disorder, purging bulimia nervosa, non-purging bulimia nervosa, or anorexia nervosa. We have used this instrument to screen for eating disorders in obese populations.

- Three Factor eating questionnaire is 21-item questionnaire, validated, to assess for emotional eating disorders and food cravings.
- Physical Activity Level - The four-item Physical Activity Stages of Change Questionnaire will be utilized to assess the physical activity level of participants. Mayo Clinic investigators, led by co-investigator Dr. Clark, have used these items to explore the relationship between quality of life and physical activity in an NCI-funded study on long-term lung cancer survivors .Physical Activity Level - The four-item Physical Activity Stages of Change Questionnaire [28] will be utilized to assess the physical activity level of participants. Mayo Clinic investigators, led by co-investigator Dr. Clark, have used these items to explore the relationship between quality of life and physical activity in an NCI-funded study on long-term lung cancer survivors [28].

- Lifestyle intervention and behavioral treatment:
  All participants will meet with a study physician as standard of care in clinical practice. All participants will guided to 1) Diet: Reduce dietary intake below that required for energy balance by consuming 1200 calories per day for women and 1400 calories per day for men; 2) Physical Activity: reach the goal of 10,000 steps or more per day; 3) Exercise: reach the goal of 150 minutes or more of cardiovascular exercise/week; 4) Limit consumption of liquid calories (i.e. sodas, juices, alcohol, etc.).

- **Visit 2: Colonoscopy #1 and Randomization**
  - Visit 2 will only be completed in the first 6 patients of each group who are willing to consent to both colonoscopy visits.
  - Visit 2 will occur 3- 5 days of Visit 1. Participants will receive a bowel prep (Movi-prep) during Visit 1 and follow standard colonoscopy preparation guides. The next day, after an overnight fasting, a colonoscopy with terminal ileum intubation will be performed. The colonoscopy will be done in the GI clinical or research unit and will be supported by sedation based on patients' characteristics (i.e., conscious sedation vs. anesthesia supported sedation). During the procedure, 8 biopsies will be obtained from the ilium, right and left colon.

  - Randomization and treatment:

Randomization will be performed by the research pharmacy upon notification by the study coordinator. Treatments will be allocated at a 1:1 ratio stratified within low, medium, or high gastric emptying (T1/2) rates, based on sex-specific thresholds. The stratification group will be determined by the study coordinator and communicated to the pharmacist. A computer application will provide the randomized assignment based on a randomization schedule created by the study statistician. Only the study statistician will have access to the complete schedule. Other study personnel and the subject will be blinded to assigned treatment.

Patients will receive study medication (active or placebo), and they will be given verbal instructions on how they should take their medications. Subjects will take medication or placebo orally twice daily on an empty stomach, 30 minutes prior to breakfast and evening dinner for 90 (+/- 5) days. Patients will be instructed to start the medication after visit 2 (colonoscopy).

- **Visit 3: Study Team visit**
  - Participants will meet with the study team (either in person at the CRTU or virtually) approximately 30 days after visit 2. The study team will assess adverse events, medication compliance, and perform a new medication dispensation (if visit is virtual the medication will be shipped to the participant's preferred address).

- **Visit 4: Study Team visit**

Participants will meet with the study team (either in person at the CRTU or virtually) approximately 30 days after visit 3. The study team will assess adverse events, medication compliance, and perform a new medication dispensation (if visit is virtual the medication will be shipped to the participant's preferred address). .

- **Visit 5: Colonoscopy #2**
  - Visit 5 will only be completed in the first 6 patients of each group who are willing to consent to both colonoscopy visits.
  - Participants will receive a bowel prep (Movi-prep) during visit 5 and follow standard colonoscopy preparation guides. The next day, after an overnight fasting, a colonoscopy with terminal ileum intubation will be performed. The colonoscopy will be done in the GI clinical or research unit and will be supported by sedation based on patients' characteristics (i.e., conscious sedation vs. anesthesia supported sedation). During the procedure, 8 biopsies will be obtained from the ilium, right and left colon.

- **Visit 6 – Exit Phenotyping**
  - Visit 6 will occur within 7 days of Visit 3. Phenotyping will be performed as at the baseline phenotyping visit including the questionnaires performed in screening visit.

Primary Endpoint:

The primary endpoint is EEC function measured through satiety hormones' (GLP-1 & PYY AUC and absolute plasma value curves) comparison between intervention and placebo groups at day 90 in APS-OB phenotype participants.

Secondary Endpoint:

Evaluation of obesity phenotypes through gastric emptying T ½ for solids, satiety sensation with a visual analogue scale (VAS), fullness (VAS), hunger (VAS), desire to eat (VAS), appetite overall score (VAS), ad-libitum buffet meal food intake (kcal), microbial changes, behavioral questionnaires, energy expenditure, and body weight in APS-OB phenotype participants intervened with IC-CBAS, compared to placebo.

Statistical Analysis:

The primary analysis will compare AUC, values between treatment and placebo groups after 90 days of IC-CBAS. Based on the previous study by Calderon et al.[1], we calculated a sample size of 36 subjects. They reported GLP-1 AUC significant difference between intervention and placebo group of 3223 mg/dl. We aim to detect a mean difference in AUC of 3223mg/dl and utilized their IQR to calculate a standard deviation of 3125mg/dl. To have 80% power to detect a difference of 3223mg/dl with a two-sample t-test would require 12 subjects per group. In order to allow for up to 30% dropout, we will enroll 36 subjects total. The effect on weight loss will be evaluated using analysis of covariance (ANCOVA) models, with relative weight loss as the dependent variable, adjusting for gastric emptying (T1/2, min) and gender. Any power lost on degrees of freedom spent on covariate parameter estimation should be more than reclaimed by reduced error variation. For the rest of the endpoints we will compare the data on gastric emptying, satiation parameters, appetite scores, body composition, energy expenditure, GI hormones, bile acids and microbiota between intervention vs. placebo, using the same ANCOVA model. Transformations will be employed as needed for heavily skewed distributions. All treatment effect estimates will be reported with 95% confidence intervals.

POTENTIAL PITFALLS AND PRECAUTIONS TAKEN:

Potential pitfalls of minor significance in this study are:

- ***Selection bias*** - Participants willing to participate will likely be more motivated to lose weight than the general population. Randomization, double blind will avoid any selection bias;

- ***Potential for type II error*** - The sample sizes have been based on appropriate statistical power with allowance for drop out. Estimates of variation have been thoroughly characterized in the prior literature from our lab; and other internal and external studies for weight loss at 12 weeks.

- ***Feasibility*** - We have identified a cohort of people in our community who have obesity, abnormal satiety phenotype, and are willing to participate. We have the experience to successfully recruit 36 participants for the study.

Human Studies Aspects

Adverse Effects of Medications: Taurocholic acid is used for gallbladder stones dissolution and prevention as a nutraceutical and food supplement. It is associated with the following potential adverse effects: nausea, diarrhea, anorexia, hypersensitivity. These are included in the consent form.

Radiation exposure: in this study comes from the ^{99m}Tc used to measure gut transit. These exposures conform to previously approved levels of radiation exposure approved by the Radiation Control Committee at Mayo Clinic. The radiation dosimetry and organ exposures (in mrad) are minimal. **See Dosimetry Table in appendix A**

ANTICIPATED RESULTS AND SIGNIFICANCE:

We expect to demonstrate that IC-CBAS restores satiety in obesity hungry gut phenotype patients, enhancing ileo colonic EEC function and subsequently inducing weight loss. This study will provide the basis for larger trials testing BA as pharmacological options in patient phenotype tailored treatment for obesity.

APPENDIX A: QUESTIONNAIRES

Bowel Disease Questionnaire

In the past 12 months, have you experienced the following?

QUESTION	YES	NO
1. 2 or less than 2 bowel movements/week		
2. Excessive straining or sensation of incomplete evacuation of stool on more than 25% of occasions		
3. Lumpy stools on more than 25% of occasions		
At least 3 months of continuous or recurrent symptoms of: 4. Abdominal pain or discomfort relieved by defecation		
5. Abdominal pain or discomfort associated with a change in stool frequency		
6. Abdominal pain or discomfort associated with a change in stool consistency		
7. More than 3 bowel movements per day		
8. Loose watery stools		
9. Bloating		
10. Swallowing difficulties		
11. Upper abdominal pain after meals more than once a month		
12. Abdominal bloating after meals		
13. Nausea regularly more than once a month		
14. Vomiting regularly more than once a month		
15. Heartburn regularly more than once a week		
16. Acid reflux regularly more than once a week		

Sign_____ **Date** _____

The Hospital Anxiety and Depression Questionnaire

Please read each item and **circle** the reply which best describes how you have been feeling during the past week. Don't devote too much time to your responses; your immediate reaction will probably be more accurate than a long thought out response.

1. I feel tense or 'wound up' :
   - Most of the time
   - A lot of the time
   - Occasionally
   - Not at all

2. I still enjoy the things I used to enjoy :
   - Definitely as much
   - Not quite so much
   - Only a little
   - Hardly at all

3. I get a frightened feeling, as if something awful is about to happen :
   - Very definitely and quite badly
   - Yes, but not too badly
   - A little, but it doesn't worry me
   - Not at all

4. I can laugh and see the funny side of things :
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

5. Worrying thoughts go through my mind :
   - A great deal of the time
   - A lot of the time
   - From time to time
   - Only occasionally

6. I feel cheerful :
   - Not at all
   - Not often
   - Sometimes
   - Most of the time

7. I can sit at ease and feel relaxed :
   - Definitely
   - Usually
   - Not often
   - Not at all

8. I feel as if I am slowed down :
   - Nearly all the time
   - Very often
   - Sometimes
   - Not at all

9. I get a frightened feeling, like 'butterflies in the stomach' :
   - Not at all
   - Occasionally
   - Quite often
   - Very often

10. I have lost interest in my appearance :
    - Definitely
    - I don't take as much care as I should
    - I may not take quite as much care
    - I take just as much care as ever

11. I feel restless as if I have to be on the move :
    - Very much indeed
    - Quite a lot
    - Not very much
    - Not at all

12. I look forward with enjoyment to things :
    - As much as I ever did
    - Rather less than I used to
    - Definitely less than I used to
    - Hardly at all

13. I get sudden feelings of panic :
    - Very often indeed
    - Quite often
    - Not very often
    - Not at all

14. I can enjoy a good book or TV program :
    - Often
    - Sometimes
    - Not often
    - Very seldom

Sign_____ **Date** _____

Bristol Stool Scale

Stool form	Appearance	Type
Separate hard lumps, like nuts (hard to pass). Result of slow transit		1
Sausage-shaped but lumpy		2
Like a sausage but with cracks on its surface		3
Like a sausage or snake – smooth and soft		4
Soft blobs with clear cut edges (easy to pass)		5
Fluffy pieces with ragged edges, a mushy stool		6
Watery, no solid pieces. Result of very fast transit		7

Circle the form which best describes your normal bowel movements.

Ease of Passage:

1. Manual disimpaction required
2. Enema or suppository required to initiate bowel movement
3. Some straining necessary to pass bowel movement
4. Easy normal passage of stool without straining
5. Urgent need to pass bowel movement spontaneously; **no** abdominal pain or discomfort present
6. Urgent need to pass bowel movement spontaneously; abdominal pain or cramping present
7. Incontinent of bowel movements

Physical Activity Stages of Change Questionnaire

For each of the questions below, please check Yes or No. Please be sure to follow the instructions carefully.

Physical activity or exercise includes activities such as walking briskly, jogging, bicycling, swimming or any other activity where the exertion is as least as hard as these activities. Your heart rate and breathing should increase.

	NO	YES
1. I am currently **physically active**		
2. I intend to become more **physically active** in the next 6 months		

For activity to be **regular**, it must add up to a **total** of **30 minutes or more per day**, and be done **at least 5 days per week**. For example, you could take one 30 minute walk, or take three 10 minute walks each day.

	NO	YES
3. I currently engage in **regular physical activity**		
4. I have been **regularly physically active** for the past 6 months		

Sign:_____ **Date:**_____

Eating Patterns Questionnaire

__ 15 1. During the past **six** months, did you often eat within any two-hour period what most people would regard as an unusually large amount of food?

1☐ Yes 0☐ No → SKIP TO QUESTION 5

__ 16 2. During the times when you ate this way, did you often feel you couldn't stop eating or control what or how much you were eating?

1☐ Yes 0☐ No → SKIP TO QUESTION 5

3. During the past **six** months, how often, on average, did you have times when you ate this way – that is, large amounts of food **plus** the feeling that your eating was out of control (there may have been some weeks when it was not present – just average those in).

__ 17

1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ Nearly every day

4. Did you usually have any of the following experiences during these occasions?

__ 18 a. Eating much more rapidly than usual? 1☐ Yes 0☐ No

__ 19 b. Eating until you felt uncomfortably full? 1☐ Yes 0☐ No

__ 20 c. Eating large amounts of food when you didn't feel physically hungry? 1☐ Yes 0☐ No

__ 21 d. Eating alone because you were embarrassed by how much you were eating? 1☐ Yes 0☐ No

__ 22 e. Feeling disgusted with yourself, depressed, or feeling very guilty after overeating? 1☐ Yes 0☐ No

5. In general, during the past **six** months, how upset were you by overeating (*eating more than you think is best for you*)?

__ 23

1☐ Not at all
2☐ Slightly
3☐ Moderately
4☐ Greatly
5☐ Extremely

6. In general, during the past **six** months, how upset were you by the feeling that you couldn't stop eating or control what or how much you were eating?

__ 24

1☐ Not at all
2☐ Slightly
3☐ Moderately
4☐ Greatly
5☐ Extremely

7. During the past six months, how important has your weight or shape been, in how you feel about or evaluate yourself as a person – as compared to other aspects of your life, such as how you do at work as a parent, or how you get along with other people?

__ 25

1☐ Weight and shape were **not very important**
2☐ Weight and shape **played a part** in how you felt about yourself
3☐ Weight and shape **were among the main things** that affected how you felt about yourself
4☐ Weight and shape **were the most important things** that affected how you felt about yourself

8. During the past **three** months, did you ever make yourself vomit in order to avoid gaining weight after binge eating?

__ 26
__ 27

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

9. During the past **three** months, did you ever take more than twice the recommended dose of laxatives in order to avoid gaining weight after binge eating?

__ 27
__ 28

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

10. During the past three months, did you ever take more than twice the recommended dose of diuretics (water pills) in order to avoid gaining weight after binge eating?

__ 29
__ 30

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

11. During the past three months, did you ever fast – not eat anything at all for at least 24 hours --in order to avoid gaining weight after binge eating?

___ 31
___ 32

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ Nearly every day

12. During the past three months, did you ever exercise for more than an hour **specifically** in order to avoid gaining weight after binge eating?

___ 33
___ 34

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

13. During the past three months, did you ever take more than twice the recommended dose of a diet pill in order to avoid gaining weight after binge eating?

___ 35
___ 36

1☐ Yes ⟶
0☐ No

How often, **on average**, was that?
1☐ Less than one day a week
2☐ One day a week
3☐ Two or three days a week
4☐ Four to five times a week
5☐ More than five times a week

Sign_____ Date _____

Multi-dimensional Body-Self Relations Questionnaire (MBSRQ)

On a scale of 1 (very dissatisfied) to 5 (very satisfied) please indicate how satisfied you are with each of the following areas or aspects of your body:

	Very dissatisfied	Mostly dissatisfied	Neither satisfied nor dissatisfied	Mostly satisfied	Very satisfied
1. Face (facial features, complexion)	1☐	2☐	3☐	4☐	5☐
2. Hair (color, thickness, texture)	1☐	2☐	3☐	4☐	5☐
3 Lower torso (buttocks, hips, thighs, legs)	1☐	2☐	3☐	4☐	5☐
4. Mid torso (waist, stomach)	1☐	2☐	3☐	4☐	5☐
5. Upper torso (chest or breasts, shoulders, arms)	1☐	2☐	3☐	4☐	5☐
6. Muscle tone	1☐	2☐	3☐	4☐	5☐
7. Weight	1☐	2☐	3☐	4☐	5☐
8. Height	1☐	2☐	3☐	4☐	5☐
9. Overall appearance	1☐	2☐	3☐	4☐	5☐

Sign_____ Date _____

EFFECT OF ILEOCOLIC-RELEASE CONJUGATED BILE ACID ON SATIETY AND ENTERO-ENDOCRINE CELL FUNCTION IN PATIENTS WITH OBESITY AND ABNORMAL SATIETY PHENOTYPE

IRB #

Food Diary

Diet: Normal Diet, Baseline

Dates:_____ to _____

Andres Acosta Cardenas, MD,
Principal Investigator

Shawna Franks
[redacted]

FOOD INTAKE DIARY – Baseline

Complete every day. Return to Mayo Clinic on visit 1.

- Please record your food, medications and beverage intake **every day**, in the table below.
- Record **everything** you eat! For example, if you add sugar to your coffee or eat a bite-sized candy, you still have to record these items.
- Make sure to include amount of food consumed. (example: 8 oz coffee, 2 tbsp peanut butter, 1 cup white rice, 12 oz steak with 2 tbsp steak sauce, 2 slices wheat bread with 1 slice american cheese, 3 pieces of salami, and 1 tsp mayonnaise.)
- If eating at a restaurant or eating prepackaged food include name of restaurant/food brand, item ordered/eaten, and amount consumed.
- If eating at a restaurant or eating prepackaged food also include calories per serving and servings consumed.

Day 1

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 2

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 3

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 4

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 5

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 6

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

Day 7

Date _____

Meal	Intake	Notes
Breakfast		
AM Snack (if any)		
Lunch		
PM Snack (if any)		
Dinner		
Other		

Participant's Signature: _____

Date:_____

AUDIT-C Questionnaire

Patient Name _____ Date of Visit _____

1. **How often do you have a drink containing alcohol?**
   - ☐ a. Never
   - ☐ b. Monthly or less
   - ☐ c. 2-4 times a month
   - ☐ d. 2-3 times a week
   - ☐ e. 4 or more times a week

2. **How many standard drinks containing alcohol do you have on a typical day?**
   - ☐ a. 0
   - ☐ b. 1 or 2
   - ☐ c. 3 or 4
   - ☐ d. 5 or 6
   - ☐ e. 7 to 9
   - ☐ f. 10 or more

3. **How often do you have six or more drinks on one occasion?**
   - ☐ a. Never
   - ☐ b. Less than monthly
   - ☐ c. Monthly
   - ☐ d. Weekly
   - ☐ e. Daily or almost daily

AUDIT-C is available for use in the public domain.

TO BE SCANNED
QUESTIONNAIRE

MAYO CLINIC

Weight Management Questionnaire

Instructions: It is very important that you fill out this questionnaire **completely**. A complete questionnaire helps your nutrition team provide the best care for you. **Return the completed form to your registered dietitian (RD) or Endocrinology provider at the time of your appointment.**

Patient Information

Mayo Clinic Number	Patient Name *(First, Middle, Last)*	Date Today *(Month DD, YYYY)*

Living Situation

☐ Alone ☐ With others, describe_____

Employment

☐ Full-time ☐ Part-time ☐ Disabled ☐ Retired ☐ Unemployed ☐ Homemaker

Weight History

How old were you when you first became overweight?

☐ 10-20 years old ☐ 20-30 years old ☐ 30-40 years old ☐ 40-60 years old ☐ greater than 60 years old

What is the most you have ever weighed?

_____pounds How old were you?_____

Can you identify significant life events when you gained weight (i.e., pregnancy, menopause, new job, etc.)?

☐ No

☐ Yes

If yes, what events? _____

What is the least you have weighed since 18 years of age?

_____pounds How old were you?_____

How long did you maintain that weight? _____months or _____years

What did you weigh (if not applicable, leave blank):

Graduating high school _____ pounds

On union/wedding day _____ pounds Age_____years old

One year ago _____ pounds

Three months ago _____ pounds

Today _____ pounds

Weight-Related Complications

Indicate which of the following weight-related conditions you are experiencing.

☐ Diabetes or elevated blood glucose

☐ Heartburn/reflux (GERD)/indigestion

☐ High blood pressure (hypertension)

☐ High cholesterol (hyperlipidemia)/Coronary artery disease (CAD)

☐ Obstructive sleep apnea (OSA) or difficulty sleeping

☐ Joint pain

☐ Asthma

☐ Other, specify _____

Family

Instructions: Indicate members of your family who are or have been overweight and whether they have experienced any of the problems listed below.

	Overweight						
	Less than 20 pounds	20 to 50 pounds	More than 50 pounds	High Blood Pressure	Diabetes or High Blood Glucose	High Cholesterol	Heart Disease
Mother	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐
Brother(s)	☐	☐	☐	☐	☐	☐	☐
Sister(s)	☐	☐	☐	☐	☐	☐	☐

Past and Current Weight Control Measures

Instructions: Complete the table below about various methods you have used to control your weight.

	Previously?		Currently?			
Methods used to control weight	**Yes**	**No**	**Yes**	**No**	**Pounds Lost**	**Pounds Regained**
Dieting on your own? If yes, briefly explain.	☐	☐	☐	☐		
"Commercial" weight loss plan/system (i.e.,Weight Watchers, Overeaters Anonymous, Atkins, other, etc.) If yes, briefly explain.	☐	☐	☐	☐		
Surgeries (weight loss). If yes, specify **date** and **type** of surgery.	☐	☐	☐	☐		
Have you ever used or engaged in the following to control your weight:						
Caffeine, "energy" drinks or pills	☐	☐	☐	☐		
"Water" pills	☐	☐	☐	☐		
Vomiting	☐	☐	☐	☐		
Laxatives	☐	☐	☐	☐		
Prolonged fasting (greater than 24 hours)	☐	☐	☐	☐		
Other_____	☐	☐	☐	☐		
Have you ever been **prescribed** medication to help control your weight (i.e., orlistat [Alli, Xenical], sibutramine [Meridia], phentermine, other)? If yes, briefly explain.	☐	☐	☐	☐		

Nutritional Supplements

Do you take nutritional supplements?

☐ No
☐ Yes If yes, describe below.

☐ Multi-vitamin/mineral

☐ Calcium
_____milligrams (mg) _____times/day

☐ Vitamin D
_____international units (IU) _____times/day

☐ Calcium plus vitamin D (combined supplement)
_____milligrams (mg) of calcium _____ international units (IU) of vitamin D _____times/day

☐ Other (herbs, extracts, protein powder/bars, fish oil) _____
_____

Physical Activity

Do you regularly exercise (i.e., go for walks, go jogging, go to a health club, go swimming)?

☐ No
☐ Yes If yes, briefly describe what you do for exercise, how often, and for how long. _____
_____

Do you often stay active doing other things (i.e., your job, yard work, farming, etc.)?

☐ No
☐ Yes If yes, briefly describe what you do, how often, and for how long. _____
_____

What do you feel are the primary factors limiting you from doing more physical activity (check all that apply)?

☐ Pain (joint, nerve) during or after physical activity
☐ Do not enjoy physical activity/boring
☐ Do not have enough time
☐ Self-conscious while being physically active
☐ Too tired/fatigued
☐ Not sure what type of activity to do
☐ Not sure how to safely be active
☐ Other. Briefly describe. _____
_____

Eating Patterns and Preparation

Have you ever talked with a registered dietitian (RD)?

☐ No
☐ Yes If yes, when and for what reason? _____
_____

How many meals do you usually eat each day?

On work days _____ On days off_____

Do you snack (eat between main meals)?

☐ No
☐ Yes How often? _____times/day
What time of day?_____
What do you usually snack on? _____
_____

Who prepares most of the food you eat?

☐ You ☐ Spouse ☐ Family Member ☐ Other, describe _____

Do you eat out at restaurants?

☐ No
☐ Yes Breakfast_____times/week Lunch_____times/week Dinner_____times/week

Eating Patterns and Preparation

Do you ever feel your eating is out of control or that you eat an excessive amount of food at one time?

☐ No
☐ Yes If yes, describe how often this occurs and what types of situations result in this behavior?_____

_____

Do you feel something other than what you eat and drink explains your difficulty controlling your weight (i.e., slow metabolism)?

☐ No
☐ Yes If yes, explain_____

_____

List the types and amounts of foods and beverages you usually eat for each of the meals/snacks listed below.

Breakfast: ☐ Yes ☐ No	**Morning Snack:** ☐ Yes ☐ No
Lunch: ☐ Yes ☐ No	**Afternoon Snack:** ☐ Yes ☐ No
Evening Meal: ☐ Yes ☐ No	**Evening Snack:** ☐ Yes ☐ No

Fill in the blanks below. About how often do you consume the various foods and beverages listed during a usual week?

Sugar, Honey, Jelly/Jam, Syrup _____ times per week Butter, Margarine, Added Oil _____ times per week Cake, Pie, Ice Cream, Candy _____ times per week	Milk *(8 ounces)* (Check one) ☐ Whole ☐ 2% ☐ 1% ☐ Skim _____ times per week Yogurt *(6-8 ounces)* _____ times per week Cheese, types_____ _____ times per week
Beef, Chicken, Pork, Lamb, Veal *(4 ounces, about the size of a deck of cards)* _____ times per week Fish *(4 ounces, about the size of a deck of cards)* _____ times per week	Vegetables *(½ cup serving)* _____ times per week
Fruit *(1 serving)* _____ times per week Fruit Juices *(6-8 ounces)* _____ times per week	Beer, Wine, Liquor *(1 serving)* _____ times per week Carbonated Beverages/Soft Drinks ☐ Diet ☐ Regular _____ times per week
Breads _____ times per week Other Starches (rice, noodles, potatoes) _____ times per week	**Food Guide** **Grains** 6 oz. per day **Vegetables** 2 ½ cups per day **Fruits** 2 cups per day **Milk** 3 Cups per day **Meat and Beans** 5 ½ oz. per day

Dosimetry per administration

Model:
Adult

RAM	Activity per administration (mCi)	Activity per administration (MBq)	Number of administrations	Organ/Wt (organ doses are in mGy) Testes 0.1	Ovaries 0.1	Breast 0.05	RBM 0.12	Lung 0.12	Thyroid 0.05	Bone 0.01	Colon 0.12	Stomach 0.12	Bladder 0.05	Liver 0.05	Esoph 0.05	Other: SI 0.025	Remainder 0.025
Tc-99m Non-Absorbable Markers (solids, oral)	0.5	18.5	1	0.02	0.48	0.01	0.09	0.02	0.00	0.09	1.85	1.09	0.13	0.08	0.01	1.13	0.07
In-111 Non-Absorbable Markers (liquid, oral)	0.05	1.85	1	0.06	0.78	0.01	0.18	0.01	0.00	0.06	2.83	0.22	0.22	0.06		0.93	0.07
Total				0	1	0	0	0	0	0	5	1	0	0	0	2	0

	Remainder organ	adrenal	brain	kidney	muscle	pancreas	SI	spleen	thymus	uterus	Weighted Average
	Mass (g)	14	1420	310	28000	100	640	180	20	80	
Tc-99m Non-Absorbable Markers (solids, oral)	Organ dose	0.07	0.00	0.12	0.07	0.20		0.14	0.01	0.30	0.07
In-111 Non-Absorbable Markers (liquid, oral)	Organ dose	0.04		0.08	0.08	0.08		0.06		0.31	0.07

E (mSv): **0.97**

Additional Comments:
Ref. - <insert reference>
In-111 non absorb. markers (liquid): Ref. ICRP 53, pg. 250.

Tc-99m non absorb. Markers (solids): Ref. ICRP 80, table 3.13.2.

Remainder are mass weighted average of named remainder organs (ICRP 60).

0 Minute

Directions: Answer each question about how you are feeling by drawing a vertical mark (|) at the appropriate point through the horizontal line of each question.

How hungry do you feel?

I am not hungry at all ——— **I have never been more hungry**

How satisfied do you feel?

I am completely empty ——— **I cannot eat another bite**

How full do you feel?

Not at all full ——— **Totally full**

How much do you think you can eat?

Nothing at all ——— **A lot**

Would you like to eat something sweet?

Yes, very much ——— **No, not at all**

Would you like to eat something salty?

Yes, very much ——— **No, not at all**

Would you like to eat something savoury?

Yes, very much ——— **No, not at all**

Would you like to eat something fatty?

Yes, very much ——— **No, not at all**

30 Minute

Directions: Answer each question about how you are feeling by drawing a vertical mark (|) at the appropriate point through the horizontal line of each question.

How hungry do you feel?

I am not hungry at all ——— **I have never been more hungry**

How satisfied do you feel?

I am completely empty ——— **I cannot eat another bite**

How full do you feel?

Not at all full ——— **Totally full**

How much do you think you can eat?

Nothing at all ——— **A lot**

Would you like to eat something sweet?

Yes, very much ——— **No, not at all**

Would you like to eat something salty?

Yes, very much ——— **No, not at all**

Would you like to eat something savoury?

Yes, very much ——— **No, not at all**

Would you like to eat something fatty?

Yes, very much ——— **No, not at all**

60 Minute

Directions: Answer each question about how you are feeling by drawing a vertical mark (|) at the appropriate point through the horizontal line of each question.

How hungry do you feel?

I am not hungry at all ——— **I have never been more hungry**

How satisfied do you feel?

I am completely empty ——— **I cannot eat another bite**

How full do you feel?

Not at all full ——— **Totally full**

How much do you think you can eat?

Nothing at all ——— **A lot**

Would you like to eat something sweet?

Yes, very much ——— **No, not at all**

Would you like to eat something salty?

Yes, very much ——— **No, not at all**

Would you like to eat something savoury?

Yes, very much ——— **No, not at all**

Would you like to eat something fatty?

Yes, very much ——— **No, not at all**

90 Minute

Directions: Answer each question about how you are feeling by drawing a vertical mark (|) at the appropriate point through the horizontal line of each question.

How hungry do you feel?

I am not hungry at all _____ **I have never been more hungry**

How satisfied do you feel?

I am completely empty _____ **I cannot eat another bite**

How full do you feel?

Not at all full _____ **Totally full**

How much do you think you can eat?

Nothing at all _____ **A lot**

Would you like to eat something sweet?

Yes, very much _____ **No, not at all**

Would you like to eat something salty?

Yes, very much _____ **No, not at all**

Would you like to eat something savoury?

Yes, very much _____ **No, not at all**

Would you like to eat something fatty?

Yes, very much _____ **No, not at all**

120 Minute

Directions: Answer each question about how you are feeling by drawing a vertical mark (|) at the appropriate point through the horizontal line of each question.

How hungry do you feel?

I am not hungry at all _____ **I have never been more hungry**

How satisfied do you feel?

I am completely empty _____ **I cannot eat another bite**

How full do you feel?

Not at all full _____ **Totally full**

How much do you think you can eat?

Nothing at all _____ **A lot**

Would you like to eat something sweet?

Yes, very much _____ **No, not at all**

Would you like to eat something salty?

Yes, very much _____ **No, not at all**

Would you like to eat something savoury?

Yes, very much _____ **No, not at all**

Would you like to eat something fatty?

Yes, very much _____ **No, not at all**

OBESITY – QUESTIONNAIRE

By: Andres Acosta

1. Current body weight:
2. Weight at graduation of high school:
3. Any particular event that produced significant weight gain? (example: pregnancy, medications)
4. Any particular reason for weight gain?
5. History of obesity in the family?
6. Number of calories consumed per day:
7. Type of macronutrient diet (High protein, high carb diet):
8. Consumption of sodas:
    - If yes, number per day
9. Consumption of artificial sweeteners:
    - If yes, number per day and which type
10. Consumption of alcohol:
    - If yes how many beverages per day
11. Do you ever drink more than four alcoholic beverages in one sitting?
12. History of smoking: Yes or no
    - If yes, how many cigarettes per day
13. How long have you been smoking
14. Any other recreational drugs?
15. Do you exercise?
16. How many times per week?
17. How many minutes per session?
18. Describe your typical week of exercise
19. Describe the exercise you did this past week.
20. What types of exercise do you do?
21. Number of minutes of exercise per week:
22. Number of steps per day:
    - What type of exercise is performed?
23. Previous attempts for weight loss:
24. Previous attempts with diet:
    - How much weight was lost?
    - How much was regained after the diet?
    - Name of the diet:
25. Any history of use of previous commercial programs? (Weight watchers)
    - Weight loss:
    - Weight regain:
    - Year:
26. Have you been on any medications for weight loss?
    a. Weight loss:
    b. Weight regain:
    c. Year:

27. Have you had any surgeries for weight loss?
    a. Weight loss:
    b. Weight regain:
    c. Year:
28. Have you had any devices for weight loss?
    a. Weight loss:
    b. Weight regain:
    c. Year:
29. Any previous history of abdominal surgeries?
30. Do you have any of the following?
    - Type 2 diabetes or pre diabetes
    - Hypertension
    - Obstructive sleep apnea or snoring
    - Weight bearing joint disease or arthritis
    - Back pain
    - Fatty liver disease or NASH
    - Depression or anxiety
    - Emotional eating or food cravings
    - Binge eating at night
    - High elevated cholesterol
    - History of coronary disease
    - History of cancer
31. Do you have any heart problems?
32. Do you have any lung problems or breathing issues?
33. Do you have any pets?
34. When you wake up in the morning, do you feel hungry?
35. What time is your first meal of the day?
36. How many meals do you have in a day?
37. Do you snack in between meals?
38. When you start eating your meals, do you feel full?
39. When you start eating your meals, do you stop when you feel full?
40. Once you have felt full, for how long do you remain full? Please answer in minutes or hours.
41. Do you have any particular food cravings throughout the day?
42. Do you have any snacks after your last meal of the day?
43. Do you consume any other beverages that have calories or artificial sweeteners?
44. Do you consume coffee?
    - If yes, how many cups a day?
45. What would be your weight loss goal?
46. When you go into a diet, which of the following do you experience?
    - Increased appetite (I'm starving throughout the day)
    - Difficulty feeling full
    - Significant cravings
    - Feeling very moody

- Feeling lack of energy
- Feeling very fatigue
- Difficulty sleeping

Activity Diary & Food diary Summary

Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM
Date________	**Dose 1:**	____:____AM	**Steps:**	__________	**Consumed Calories (solid):**	________	**Consumed Calories (liquid):**	________	**Exercise:**	_______ min	**Dose 2:**	____:____PM

Physical exam and Medical history **IRB#:** 21-008310

MC #:

Name:
DOB:

HPI:
Race:

Meds:
(__see attached)

Allergies:

Menstrual Hx:

Childbearing? Y or N

If no:_____

PMH/PSH:

FMH:

Social:

PE:
Ht: Wt. BMI:

BP:

P: R: T:

PE: System review:

General: Well appearing and in no acute distress
Skin: No rashes or blemishes
Head: Normocephalic
Eyes: Pupils equal, round and reactive to light
ENT: Normal oropharynx and external nose and ears normal
Neck: No thyroid masses or thyromegaly
Lymph: No cervical, inguinal, axillary lymphadenopathy
Heart: Normal S1, S2 without murmur, rub or gallop
Lungs:
Abdomen/GI: Nontender, soft, bowel sounds present. No hepatosplenomegaly.
Musculoskeletal: No joint effusion, edema or erythema
Extremities: No edema
Rectal:
Neurological:
Psychological:
Other:

Activity Tracker Instructions

HOW DO I CREATE A FITBIT ACCOUNT AND CONNECT MY DEVICE?

The Fitbit app is compatible with most popular phones and tablets, as well as Windows 10 computers. To verify that your phone or tablet is compatible with the Fitbit app, go to [redacted]

If your phone or tablet isn't compatible, and you don't have a Windows 10 computer, you can set up some Fitbit devices on a Mac or Windows 8.1 computer with a program called Fitbit Connect.

Choose a link below depending on whether you prefer to set up your device with the Fitbit app or with Fitbit Connect.

- [redacted]
- [redacted]

FITBIT APP

Note: If you're setting up Fitbit Charge 4 or Fitbit Versa 2 with an Android phone, a notification appears on your phone to begin the setup process. Tap the notification and follow the on-screen instructions to set up your device. If you don't have the Fitbit app, the notification takes you to the Google Play Store to download the app.

To set up your Fitbit device with the Fitbit app:

1. Download and install the Fitbit app from one of the following locations:
    - Apple devices—[redacted]
    - Android devices—[redacted]
    - Windows 10 devices (phones, tablets, and computers)—[redacted]

Note that you need an account with the store before you can download apps.

2. Open the Fitbit app and tap **Join Fitbit**.
    - The email address for your account is: _____
    - The Password for your account is: _____[redacted]_____ - please use this password, and be upper/lower case sensitive.
    - Please DO NOT change either of these for the duration of the study.
3. Follow the on-screen instructions to create a Fitbit account and connect ("pair") your Fitbit device to your phone or tablet. Pairing makes sure your Fitbit device and phone or tablet can communicate with one another (sync their data).

Note that to create a Fitbit account, you're prompted to enter your birthdate, height, weight, and sex to calculate your stride length and to estimate distance, basal metabolic rate, and calorie burn. For more information, see [redacted] After you set up your account, your first name, last initial, and profile picture are visible to all other Fitbit users. You have the option to share other information, but most of the information you provide to create an account is private by default.

FITBIT DEVICE CONNECT

If you don't have a compatible phone or tablet, you can set up and sync most Fitbit devices on your computer with Fitbit Connect. Fitbit Connect is a free software application that lets your Fitbit device sync its data with your fitbit.com dashboard. To learn more about the fitbit.com dashboard, see [redacted]

If your computer isn't Bluetooth-enabled, you must use a wireless sync dongle to set up and sync your Fitbit device. Most Fitbit devices don't come with a dongle, but you can buy one from the Fitbit Store. We recommend using the Fitbit app if you can.

To install Fitbit Connect and set up your device:

1. If your computer isn't Bluetooth-enabled, insert a wireless sync dongle into a USB port on your computer.
2. Go to [redacted]
3. Scroll down and click the pink **Download** button.
4. After the download completes, double-click the downloaded file to start installation.
5. After installing, when prompted, choose **Set up a New Fitbit Device**.
6. Follow the on-screen instructions to create a Fitbit account and connect your device.

Note that the personal information you provide during setup is used to calculate your basal metabolic rate (BMR), which helps determine your estimated calorie expenditure and your body mass index (BMI). For more information, see [redacted] This information is private unless you change your privacy settings and opt to share it with your Fitbit friends.

If you have trouble, see [redacted]

Your device should come in the mail. Open the box, take out the tracking device, power it up and link it to your mobile device.

- You will be sent weekly diaries to fill in data collected through the fit bit app. If you have any troubles navigating the app you can contact the clinical research coordinator with whom you have been in contact.

Directions:

Wear your device all day and night, regardless of how active or inactive you are. All the information it is collecting throughout the day is important to us! Remove the device to charge it, try to do this during periods of inactivity or overnight.

Sync your device to your account at least every 2-3 days. You can do this by using the app on your phone, or by connecting the device to your computer and logging in to your account.

Please use any and all of the features on the device however you would like. This includes the food intake diaries, activity tracking and sleep tracking.

If you have any questions regarding your Fitbit or the account please email [redacted]

REFERENCES:

1. Calderon, G., et al., *Ileo-colonic delivery of conjugated bile acids improves glucose homeostasis via colonic GLP-1-producing enteroendocrine cells in human obesity and diabetes.* EBioMedicine, 2020. **55**: p. 102759.
2. Acosta, A., M. Camilleri, and D. Burton, *Exenatide in obesity with accelerated gastric emptying: a randomized, pharmacodynamics study*. Vol. 3. 2015.
3. Hales, C.M., et al., *Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018.* NCHS Data Brief, 2020(360): p. 1-8.
4. H. Waters, M.G., *America's obesity crisis: the health and economic costs of excess weight*
5. Jiang, J., et al., *Association of obesity with cardiovascular disease mortality in the PLCO trial.* Preventive Medicine, 2013. **57**(1): p. 60-64.
6. Sun, Y., et al., *Association of Normal-Weight Central Obesity With All-Cause and Cause-Specific Mortality Among Postmenopausal Women.* JAMA Network Open, 2019. **2**(7): p. e197337-e197337.
7. Cifuentes, L., M. Camilleri, and A. Acosta, *Gastric Sensory and Motor Functions and Energy Intake in Health and Obesity—Therapeutic Implications.* Nutrients, 2021. **13**(4): p. 1158.
8. Acosta, A., et al., *Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic.* Obesity (Silver Spring), 2021. **29**(4): p. 662-671.
9. Gonzalez-Izundegui, D., et al., *Association of Gastric Emptying with Postprandial Appetite and Satiety Sensations in Obesity.* Obesity, 2021.
10. Gonzalez-Izundegui, D., S. Singh, and A. Acosta, *Food intake regulation: Relevance to bariatric and metabolic endoscopic therapies.* Techniques and Innovations in Gastrointestinal Endoscopy, 2020.
11. Acosta, A., et al., *Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy.* Gastroenterology, 2015. **148**(3): p. 537-546 e4.
12. Abu Dayyeh, B.K., et al., *Endoscopic Sleeve Gastroplasty Alters Gastric Physiology and Induces Loss of Body Weight in Obese Individuals.* Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association, 2017. **15**(1): p. 37-43 e1.
13. Gomez, V., G. Woodman, and B.K. Abu Dayyeh, *Delayed gastric emptying as a proposed mechanism of action during intragastric balloon therapy: Results of a prospective study.* Obesity, 2016. **24**(9): p. 1849-53.
14. Halawi, H., D. Khemani, and D. Eckert, *Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial*. Vol. 2. 2017. 890-99.
15. Lopez-Nava, G., et al., *Personalization of Endoscopic Bariatric and Metabolic Therapies Based on Physiology: a Prospective Feasibility Study with a Single Fluid-Filled Intragastric Balloon.* Obes Surg, 2020.
16. Vargas, E.J., et al., *Accelerated gastric emptying is associated with improved aspiration efficiency in obesity.* BMJ Open Gastroenterol, 2019. **6**(1): p. e000273.
17. Camilleri, M., *Peripheral mechanisms in appetite regulation.* Gastroenterology, 2015. **148**(6): p. 1219-33.
18. Parks, D.J., et al., *Bile acids: natural ligands for an orphan nuclear receptor.* Science, 1999. **284**(5418): p. 1365-8.
19. Simmonds, W.J., A.F. Hofmann, and E. Theodor, *Absorption of cholesterol from a micellar solution: intestinal perfusion studies in man.* J Clin Invest, 1967. **46**(5): p. 874-90.
20. Mekhjian, H.S., S.F. Phillips, and A.F. Hofmann, *Colonic absorption of unconjugated bile acids.* Digestive Diseases and Sciences, 1979. **24**(7): p. 545-550.
21. Camilleri, M. and G.J. Gores, *Therapeutic targeting of bile acids.* American journal of physiology. Gastrointestinal and liver physiology, 2015. **309**(4): p. G209-15.
22. Wu, T., et al., *Effects of taurocholic acid on glycemic, glucagon-like peptide-1, and insulin responses to small intestinal glucose infusion in healthy humans.* J Clin Endocrinol Metab, 2013. **98**(4): p. E718-22.
23. Kars, M., et al., *Tauroursodeoxycholic Acid May Improve Liver and Muscle but Not Adipose Tissue Insulin Sensitivity in Obese Men and Women.* Diabetes, 2010. **59**(8): p. 1899-1905.

24. Rudling, M., *Understanding mouse bile acid formation: Is it time to unwind why mice and rats make unique bile acids?* J Lipid Res, 2016. **57**(12): p. 2097-2098.
25. de Bruïne, A.P., et al., *NCI-H716 cells as a model for endocrine differentiation in colorectal cancer.* Virchows Arch B Cell Pathol Incl Mol Pathol, 1992. **62**(5): p. 311-20.
26. Bush, K., et al., *The AUDIT Alcohol Consumption Questions (AUDIT-C): An Effective Brief Screening Test for Problem Drinking.* Archives of Internal Medicine, 1998. **158**(16): p. 1789-1795.
27. Spitzer, R., S. Yanovski, and M. Marcus, *The questionnaire on eating and weight patterns-revised (QEWP-R).* New York: New York State Psychiatric Institute, 1993.
28. Solberg Nes, L., et al., *Physical activity level and quality of life in long term lung cancer survivors.* Lung Cancer, 2012. **77**(3): p. 611-6.