Effects of Liraglutide on Gastric Functions and their Relationship to Weight Loss in Obesity

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ABSTRACT

Obesity prevalence continues to increase worldwide; 69% of U.S. adults are overweight or obese. Despite advances in understanding obesity pathophysiology, weight loss with current non-surgical treatments (diet and medications) is highly variable, and predictors of weight loss with obesity pharmacotherapy are unknown. In studies funded by RO1-DK67071 in 509 participants, obesity was associated with greater fasting gastric volume, accelerated gastric emptying (solids and liquids), lower postprandial peak plasma PYY, and greater calories consumed to achieve satiation (volume to fullness) and to evoke satiety with an ad-libitum meal. We showed that a short-acting GLP-1 agonist, exenatide, 5µg, SQ, BID for 30 days, delays gastric emptying and induces weight loss. Thus, quantitative gastrointestinal (GI) traits are associated with higher BMI, distinguish obesity phenotypes, and may predict efficacy of obesity drug therapy. In the R56-DK67071-funded pilot randomized, placebo-controlled trial of the longer-acting GLP-1 agonist, liraglutide, 3mg, SQ daily, we showed: (a) feasibility to recruit and randomize, over 8 months, 30 patients into a 4-month study (only 2 dropouts on treatment, to date); (b) safety data in all 30 randomized patients; (c) baseline quantitative traits of gastric emptying of solids and liquids, fasting and postprandial gastric volumes; satiation and satiety data; postprandial plasma incretins (GLP-1 and PYY) in all randomized patients; (d) gastric emptying data at fully escalated dose of liraglutide (weeks 5-6) in 30 patients; (e) repeat measurement (as in c) of quantitative traits at 16 weeks' treatment in 28 patients; (f) monthly weight data for duration on treatment in 28 patients.

Our *overall hypothesis* is that weight loss with pharmacological agents may be individualized, based on specific abnormalities in quantitative GI traits. We propose a randomized, controlled clinical and pharmacodynamics trial, using a 2-treatment stratified design, to assess the hypothesis that a quantitative trait (gastric emptying rate) can impact the weight loss response among overweight (BMI $\geq$27kg/m^2 plus obesity co-morbidities) or obese (BMI $\geq$30kg/m^2) patients to treatment with the FDA-approved GLP-1 receptor agonist, liraglutide (dose escalated to maximum of 3mg, SQ, per day for 12 weeks) compared to placebo. Effects will be compared for those with baseline accelerated in comparison with normal gastric emptying.

Our *aims* are: first, to assess the effects of liraglutide, 3mg/day, on gastric motor functions, satiation, satiety, weight loss and incretins; and second, to appraise the association of baseline accelerated gastric emptying on weight loss in response to liraglutide treatment. By measuring quantitative GI traits at baseline and after 12 weeks of liraglutide treatment, we shall further understand the mechanism of action of this GLP-1 agonist. As an exploratory assessment, we shall measure stiffness and fat content of liver at three different time points during the study: baseline, week 8, and week 16 of treatment in the 2 treatment groups.

Significance: Our study addresses the treatment of obesity, introducing an era of individualizing drug therapy for obesity based on quantitative biomarkers. Therefore, it addresses an important public health challenge.

APPROACH: GENERAL METHODS

Overall Design, Randomization and Allocation

We shall perform a placebo-controlled, parallel-group trial of liraglutide for a treatment period of 3 months after achieving the target dose (3mg QD) following dose escalation. All participants will undergo baseline measurements of GI, behavioral and psychological traits. *These assessments are needed to evaluate potential confounders that may interact with the effects of liraglutide on the endpoints in these studies.* Randomization will be stratified on gender, BMI, and GE of solids (accelerated or normal). Overweight or obese patients with delayed GE of solids will be excluded from the trial with liraglutide, given the theoretical risk of induction of symptomatic gastroparesis as a result of further delay in GE. All patients will be randomized to active drug or placebo. Once participants are randomized, the doses and dose escalation (on active drug) will be the same for all subjects, except for delayed dose escalation in patients who cannot tolerate the standard titration (0.6mg per week). A computer generated randomization schedule generated by the study statistician's office will be submitted to the Mayo Clinic CCaTS Research Pharmacy.

Allocations will be concealed; studies will be blinded until data are transmitted to the statistician for data lock.

Selection of Overweight and Obese Participants

We plan to study a cohort of *112* patients (using 2-treatment stratified design) with BMI >30kg/m^2 or >27kg/m^2 with an obesity-related co-morbidity [e.g. type 2 diabetes mellitus (T2DM) on metformin monotherapy or diet alone, hypertension, hyperlipidemia, obstructive sleep apnea]. We have already genotyped and obtained baseline quantitative trait measurements of interest [GE of solids, kcal intake at buffet meal, and glycemia indices in obese patients with hyperglycemia (T2DM receiving metformin)] in almost 500 patients residing within 75 miles of Mayo Clinic in Rochester, MN. Over 80% of these patients reside within 25 miles of Rochester, MN. Anticipating 20% drop out from the study (Lean et al. 2014), we will screen *160* patients to ensure *112* enter the 16 weeks' trial of liraglutide, 3mg SQ daily versus placebo, analyzed using ITT principles.

Inclusion criteria:

a. Overweight and obese adults (>30kg/m^2 or >27kg/m^2 with an obesity-related co-morbidity) residing within 125 miles of Mayo Clinic in Rochester, MN; these will be otherwise healthy individuals with no unstable psychiatric disease and not currently on treatment for cardiac, pulmonary, gastrointestinal, hepatic, renal, hematological, neurological, or endocrine (other than hyperglycemia or T2DM on metformin) disorders.

b. Age: 18-65 years.

c. Gender: Men or women. *We shall recruit equal proportions of men and women*. Women of childbearing potential will be using an effective form of contraception and have negative pregnancy tests within 48 hours of enrollment and before each radiation exposure. In addition, since liraglutide is classified as Pregnancy Category X, monthly urine pregnancy testing will be performed in any female participant with childbearing potential.

Exclusion criteria:

a. Weight exceeding 137 kilograms (safety limit of camera for measuring gastric volumes)

b. Abdominal surgery other than appendectomy, cholecystectomy, Caesarian section or tubal ligation

c. Positive history of chronic GI diseases, systemic disease that could affect GI motility, or use of medications that may alter GI motility, appetite or absorption, e.g., Orlistat

d. Patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia II

e. *Past or current history of pancreatitis, gallstones, history of alcoholism, blood triglyceride levels > 500mg/dL*

f. Significant untreated psychiatric dysfunction (Clark et al. 2007, Cunningham et al. 2012) based upon screening with the Hospital Anxiety and Depression Inventory [HAD (Zigmond & Snaith 1983)], a self-administered alcoholism screening test [AUDIT-C (Bush et al. 1998)], and the Questionnaire on Eating and Weight Patterns-Revised [splurge eating disorders and bulimia (Yanovski et al. 2015)]. If such a dysfunction is identified by a HAD score >11 on either the Anxiety or Depression subscales or difficulties

with substance or eating disorders, the participant will be excluded and given a referral letter to his/her primary care doctor for further appraisal and follow-up treatment.
g. Intake of any medication (except multivitamins) within 7 days of the study. Exceptions are birth control pill, estrogen and thyroxine replacement therapy, and any medication administered for co-morbidities as long as they do not alter GI motility including GE and gastric accommodation. For example, statins for hyperlipidemia, diuretics, β-adrenergic blockers, ACE inhibitors and angiotensin antagonists for hypertension, and metformin for T2DM or prediabetes are permissible. In contrast, resin sequestrants for hyperlipidemia (Psichas et al. 2012), α2-adrenerigc agonists for hypertension, or other GLP-1 agonists (exenatide) or amylin analogs (pramlintide) *or DPP-IV inhibitors* are not permissible since they significantly affect gastric functions or appetite.
h. Delayed gastric emptying at 2 and 4 hours
i. Hypersensitivity to liragutide
j. Participate in *highly intense physical activity* program that could potentially interfere with study interpretation

Baseline Primary Quantitative Trait Relevant to Effect of Liraglutide: Gastric Emptying

At baseline, **GE of solids** will be measured and participants characterized as having accelerated GE [$T_{1/2}$ of solids <93min in females, <78min in males (Camilleri et al. 2012)] or normal GE (see 10^{th}-90^{th} percentile in **Table 5**). Patients with delayed GE of solids (>90^{th} percentile according to gender) will be excluded, since it is unethical to potentially induce gastroparesis or significantly increase the delay in GE with a GLP-1 agonist in patients with baseline abnormal GE of solids. Note that gender, but not age or BMI, was associated with GE of solids (GE $T_{1/2}$, and proportion emptied at 1h and 2h, all $p<0.001$) in healthy controls (Camilleri et al 2012).

Table 5. GE in healthy controls using identical method to that in application (Camilleri et al 2012).

Data show mean ± SD	**All controls, n=319**	**Male controls, n=104**	**Female controls, n=215**
Age , y	36.2 ± 13.1	34.6 ± 13.3	37.2 ± 12.8
BMI, kg/m^2	26.9 ± 5.1	27.8 ± 4.5	26.5 ± 5.3
Solid GE $T_{1/2}$,	121.7 ± 29.8	109.9 ± 28.6	127.7 ± 28.7

Baseline Characterization of Secondary Quantitative Traits Relevant to the Effects of Liraglutide

At baseline, we shall also measure gastric volume (fasting and post-300kcal Ensure® drink), satiation (volume to fullness and MTV by Ensure® drink test, that is, the kcal intake under constant nutrient liquid intake 30kcal/min), appetite/satiety (kcal intake at an *ad libitum* buffet meal, which will be summarized henceforth as "satiety"), and plasma GLP-1 and PYY during fasting and at 15, 30, 45, and 90 minutes after the start of ingestion during Ensure® drink test. Further details of these measurements are provided below.

These measurements are essential to **ensure that the study stratifies patients based on GE and appraises the effect of liraglutide on the quantitative traits that impact satiation and satiety.**

Baseline and monthly measurements will be taken of hip-waist ratio, DEXA body composition (only at baseline and end of study), height, weight, blood pressure, pulse, and fasting blood glucose. The monthly measurements will also serve to enhance compliance and ongoing standardization of behavioral treatment.

Standardization of Behavioral Treatment

Under the supervision of Matthew Clark, Ph.D., co-investigator and staff behavioral interventionist [as in our behavioral protocols in previous clinical trials (Vazquez-Roque et al. 2007, Grudell et al. 2008)] and in a weight regain intervention (Himes et al 2015), we will standardize for potential differences in behavioral aspects of weight reduction therapy. All participants will be given a standard text ("LEARN" Manual, 10^{th} ed.) for guidance on healthy lifestyle changes (Brownell 2004) and will meet at baseline and approximately weeks 4, 8 and 12 with a behavioral intervenionist who has expertise in obesity treatment. Under the guidance of Matthew M. Clark, PhD, the behavioral interventionists (master's or doctoral level psychologist, a registered nurse, and a bachelor's level study coordinator) will provide brief behavioral

counseling for weight management to study participants. Study team members will be trained in behavioral interventions through leading or observed a 12 week clinical weight management group sessions provided by the Department of Psychiatry and Psychology. Upon approval by Dr. M. Clark, these study team members will deliver behavioral interventions independently to active participants of this study. Dr. Clark meets with the study interventionists monthly to provide ongoing feedback and guidance.

The behavioral interventionists will follow a session outline to standardize session content. Study participants will be taught a range of behavioral skills for successful weight management. These will be 15 to 20 minute, standardized counseling sessions that incorporate motivational interviewing strategies. To maintain treatment fidelity, the psychologists will then complete visit forms documenting the content of the completed counseling session. Additionally, study participants will have brief (10min) contact with a member of the study team approximately every 4 weeks to inquire about their adherence to study protocol, any difficulties they are experiencing, whether they are reading the LEARN Manual (**Table 6**), and to answer any additional questions arising from their reading and lifestyle change. At each study visit, adherence to medication intake will be assessed, and body weight and automated blood pressure will be recorded in the Mayo Clinical Research Unit. In previous studies (Levine et al. 2005), we have provided study participants with recognition to demonstrate our appreciation for their time and to reduce study attrition. At week 8, participants will receive a token of thanks (Mayo Clinic water bottle) and at week 16, a copy of the book, The Mayo Clinic Diet.

Table 6. Content of counseling sessions and LEARN Manual assignments

	Discussion and Values	**Reading assigned**
1	a. introduce the LEARN manual; b. discuss the concept of readiness for change; c. differences between lifestyle change and diet highlighted; d. value of keeping food records, identifying eating triggers, and e. importance of eating 3 scheduled meals per day	chapters 1-4 of the LEARN manual prior to next visit
2	a. review chapters 1-4 of the LEARN manual; b. eating triggers, the benefits of physical activity, and problem solving strategies	chapters 5-8 of the LEARN manual
3	a. review chapters 5-8 of the LEARN manual; b. role of social support for health behavior changes; c. strategies for goal setting and controlled eating	chapters 9-12 of the LEARN manual
4	a. review chapters 9-12 of the LEARN manual, b. review progress in physical activity and meal planning; c. strategies to challenge negative thinking and relapse prevention techniques	

After September 7, 2018, the MAYO CLINIC DIET BOOK will be used exclusively since the LEARN manual is no longer available.

Session	**Discussion and Values**	**Reading assigned**
1	Introduce the Mayo Clinic Diet book: Chapter 1, Ready Set Go; Chapter 2, Add Five Habits; Chapter 5, What Have You Learned; Chapter 6, The Next Phase; Chapter 7, Know Your Goals; Chapter 11, Track Your Progress	Chapters 1, 2, 5, 6, 7, 11
2	Review chapters previously assigned: Chapter 3, Break Five Habits; Chapter 4, Adopt Five Bonus Habits; Chapter 10, Expand Your Activity Plan	Chapters 3, 4, 10
3	Review chapters previously assigned: Chapter 8, Set Your Targets; Chapter 9, Create Your Eating Plan; Chapter 12, Seek Support	Chapters 8, 9, 12
4	Review chapters previously assigned: Chapter 13, What's Your Healthy Weight; Chapter 14, Energy Calories and Weight; Chapter 15, The Mayo Clinic Healthy Weight Pyramid; Chapter 16 Making Meals Easier; Chapter 17, Eating Out; Chapter 18, How to Change Behaviors; Chapter 19, Burning Even More Calories; Chapter 20, I Slipped Up-What Do I Do?	Chapters 13-20

Questionnaires to Assess GI Symptoms and Affective Disorders

Participants will complete a series of questionnaires (all included in the APPENDIX): GI symptoms with the validated Bowel Disease Questionnaire (Talley et al. 1989), the Psychosomatic Symptom Checklist to assess the level of somatization, and the Hospital Anxiety and Depression Inventory (Zigmond & Snaith

1983) to appraise the contribution of affective disorder, *which may confound assessment of weight effects of liraglutide.*

Questionnaires to Exclude Addiction and Psychiatric Eating Disorders *(potential confounders of weight effects of liraglutide)*

a. **AUDIT-C Alcoholism Screening Test** (Bush et al. 1998) - 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 will be reviewed by study personnel, and in women, a score of 3 or more will be reviewed by study personnel. However, when the points are above recommended limits, the provider will review patient's alcohol intake over past few months to confirm accuracy.

b. **Eating Disorders Questionnaire** - The **Questionnaire on Eating and Weight Patterns-5 (QEWP-5, Appendix 7)** (Yanovski et al. 2015) is a valid measure of screening for eating disorders which has been used in its different iterations since 1993 (Yanovski 1993) in several national multi-site field trials. Respondents are classified as binge eating disorder or bulimia nervosa. We have used this instrument to screen for eating disorders in obese populations (Vazquez-Roque et al. 2007). Since the QEWP-5 may not be sufficiently sensitive and specific to rule out binge eating disorder, based on a gold-standard diagnostic interview (de Zwaan et al. 1993), we shall be most careful to rule out binge eating disorder via **clinical interview** (with the expertise of Dr. Matthew Clark), since this important phenotype has been shown to have an impact on energy intake in laboratory studies (Walsh et al. 2003) and on gastric size (Geliebter et al. 2004). In a community sample, we found an association with binge eating patterns and GI symptoms (Cremonini et al. 2009). We will also administer the QEWP-5 for DSM-5 criteria assessment.

c. **Body Image Satisfaction** - **The Multidimensional Body-Self Relations Questionnaire** (Brown et al. 1990) provides a standardized attitudinal assessment of body image, normed from a national body-image survey (Cash et al. 1986). Items are rated on a 5-point scale, ranging from 1=Definitely Disagree to 5=Definitely Agree. In this study, we will use one of the sub-scales, *the Body Areas Satisfaction Scale*, which measures feelings of satisfaction with discrete aspects of physical appearance (e.g., face, weight, hair). Cronbach's α values range from .70 to .89 (Cash 1994).

d. **Eating Behaviors - The Weight Efficacy Life-Style Questionnaire** [WEL (Clark et al. 1991; Batsis et al. 2009; Ames et al. 2015)] is a 20-item eating self-efficacy scale consisting of a total score and five situational factors: negative emotions, availability, social pressure, physical discomfort, and positive activities. Subjects are asked to rate their confidence about being able to successfully resist the urge to eat using a 10-point scale ranging from 0=not confident to 9=very confident.

e. **Physical Activity Level** - The four-item **Physical Activity Stages of Change Questionnaire** (Marcus et al. 1982) will be utilized to assess the physical activity level of participants. Mayo Clinic investigators, led by co-investigator Dr. Matt Clark, have used these items to explore the relationship between quality of life and physical activity in long-term lung cancer survivors (Clark et al. 2008, Solberg Nes et al. 2012).

Study Medication: Liraglutide, *a Longer-Acting GLP-1 Receptor Agonist*

Introduction: Whereas, liraglutide is approved for the treatment of obesity (or overweight with co-morbidities), these data are based on large multicenter studies in which the average weight loss was only about 5.6kg over placebo (mean weight loss from baseline 8.4kg) with 12-56 weeks of treatment (Pi-Sunyer et al. 2015).

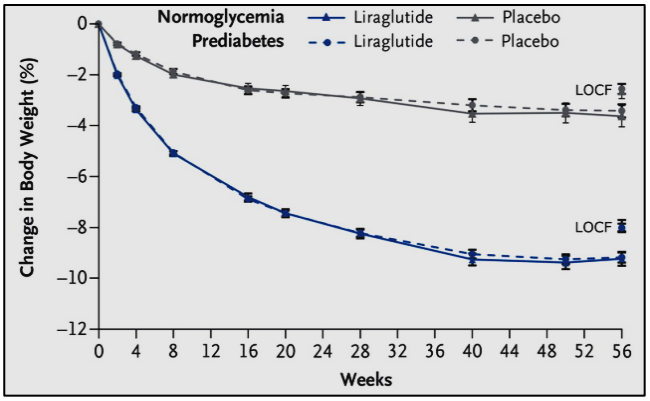

Figure 6. Effect of liraglutide vs. placebo on weight loss in multicenter study of Pi-Sunyer et al. 2015

Almost 20% of patients treated with liraglutide developed adverse events including acute, severe abdominal pain or acute pancreatitis and, more commonly, nausea and vomiting that led to either discontinuation or failure to reach the full dose of 3mg daily after the first 4 weeks of dose escalation required in the trial. Moreover, another multicenter study showed that liraglutide produced small but statistically significant improvements in several cardiometabolic risk factors compared with placebo (Wadden et al. 2013). Given the fact that the multicenter studies may include nonuniform cohorts (e.g. the Pi-Sunyer study included 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia), *studies that explore MECHANISMS of action of the medication require standardized, validated methods. We propose a single-center study in our lab at Mayo Clinic because of the extensive experience and validation of all the quantitative traits [including one study of 509 participants (Acosta et al. 2015)], ensuring eligibility of participants and characterization of behavioral traits (which are potential confounders.* The **feasibility of the proposed, unique studies** are demonstrated in our **preliminary data with liraglutide 3mg**.

Prior Reports of Effects of Liraglutide on Gastric Functions Are Inconclusive

(i). Horowitz et al. (2012) showed in patients with T2DM that liraglutide, up to 1.8mg dose, resulted in retardation of liquid GE, since it was measured by plasma acetaminophen method.

(ii). Rotondo et al. (2013) showed that 0.6mg liraglutide had no effects on gastric perception, compliance or satiation, but it inhibited gastric accommodation measured by balloon in 10 healthy controls with normal BMI.

(iii) Van Can et al. (2014) studied effects of once daily liraglutide, 1.8mg, 3.0mg, or placebo, in a double-blind, incomplete crossover, 5-week trial on GE, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. They showed reductions in 1-hour GE of 23% with liraglutide, 3.0 mg, and 13% with 1.8mg compared to placebo. Given the method used to measure GE (plasma acetaminophen), the study could only appraise GE of liquids, and the effect of the GLP-1 agonist was only demonstrable in the first hour. It is not surprising that the 5-hour AUC was not different between liraglutide and placebo, since, over that period, all the acetaminophen should be emptied from the stomach and absorbed in the normal small bowel.

Thus, prior PUBLISHED studies are inconclusive, and effects of 3mg liraglutide on GE solids in short term (5 wk) and at 16 wks were unknown, other than the preliminary data from our pilot study.

Approval status by FDA (December 23, 2014): Liraglutide is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with BMI of ≥30 kg/m^2 (obesity) or a BMI of ≥27 kg/m^2 (overweight) with ≥1 weight-related condition (e.g., hypertension, T2DM, dyslipidemia).

Dosing recommendations: Initiate at 0.6mg S.C. daily for 1 week; increase by 0.6mg/day in weekly intervals until a dose of 3mg/day is achieved.

Supply: Liraglutide (3mg SQ injection) and placebo will be dispensed by Mayo Clinic Research Pharmacy. *As in the pilot study, all supplies will be dispensed by the pharmacy staff at a site away from the Clinical Research Unit and the study staff.*

Randomization: The randomization schedule will be generated before the start of the study in the Section of Biostatistics, Mayo Clinic, and will be given to the research pharmacist. Medications will be stored in a

monitored, climate-controlled environment according to manufacturer's directions. Monitoring records will be available for review to ensure quality control.

Medication dispensing and delivery: Medications will be dispensed and delivered in such a manner that (a) all study personnel, nurses and technicians in the Clinical Research Unit, (b) the study staff and investigators directly involved in this research, and (c) the participants will be blinded to the nature of the study medication. The nursing personnel of the Clinical Research Unit will dispense the medication guide instructions and will provide the subject education on the proper administration of the study medication prior to start of dosing. A "Direction for Use" pamphlet will be given to subjects, who will be instructed how to use liraglutide and placebo.

Quantitative Traits

On different days, participants will attend the Mayo Clinic Clinical Research Trials Unit (CRTU) at scheduled time after an 8-hour fasting period, and the following validated quantitative traits will be measured:

1. **GE of solids** by scintigraphy: The primary endpoint is gastric half-emptying time (GE $T_{1/2}$), and the secondary endpoints are proportions emptied at 2 and 4 hours (Vazquez-Roque et al. 2006). The normal range for GE $T_{1/2}$ is based on 10^{th} and 90^{th} percentiles in healthy volunteers, based on gender (see Table *5*, Camilleri et al. 2012). In general, GE of liquids is non-contributory in the context of postprandial symptoms (Sachdeva et al. 2011); in order to reduce radiation burden (needing two isotopes to assess both liquid and solid emptying), we will study exclusively GE of solids.
2. **Fasting and postprandial Gastric Volume (GV)** by single photon emission computed tomography (SPECT), developed and validated (including performance characteristics) in our lab (Bouras et al. 2002; Delgado-Aros et al. 2005; Breen et al. 2011).
3. **Satiation** by **Ensure® nutrient drink test** (1kcal/mL, 11% fat, 73% carbohydrate, and 16% protein) ingested at a constant rate of 30ml/min to measure volume to fullness (VTF) and maximal tolerated volume, MTV (Chial et al. 2002). Briefly, participants record their sensations every 5 minutes using a numerical scale from 0 to 5, with level 0 being no symptoms, level 3 corresponding to fullness sensation after a typical meal (VTF) and level 5 corresponding to the MTV (maximum or unbearable fullness/satiation). Nutrient intake is stopped when subjects reach the score of 5. Postprandial symptoms of fullness, nausea, bloating,
and pain are measured 30 minutes after the meal using 100 mm horizontal visual analog scales, with the words "none" and "worst ever" anchored at each end.
4. **Satiety (for assessment of kcal intake as a measure of appetite)** by ad-libitum buffet meal to measure total caloric intake and macronutrient distribution in the chosen food (Vazquez-Roque et al. 2006). Five hours after ingesting 300 mL liquid nutrient (Ensure®) as part of the SPECT gastric volume study, participants will be invited to eat, during a 30-minute period, a standard *ad libitum* meal that includes:

a. standardized lasagna meal (Stouffers, Nestle USA, Inc, Solon, OH; nutritional analysis of each 326-g box: 420 kcal, 17 g protein [16% of energy], 38 g carbohydrate [37% of energy], and 22 g fat [47% of energy]; vanilla pudding (Hunts, Kraft Foods North America, Tarrytown, NY; nutritional analysis of each 99-g carton: 130 kcal, 1 g protein [3% of energy], 21 g carbohydrate [65% of energy], and 4.5 g fat [32% of energy]); and

b. skim milk (nutritional analysis of each 236-mL carton: 90 kcal, 8 g protein [36% of energy], 13 g carbohydrate [64% of energy], and 0 g fat).

The total amount (grams and kilocalories) of food consumed and the kilocalories of each macronutrient at the ad libitum meal were analyzed by using validated software (ProNutra 3.0; Viocare Tech. Inc., Princeton, NJ).

Overweight or obese participants will be subdivided into "excessive eaters" [the top tertile (1176 kcal) as defined in a prior study of 264 participants] and the bottom 2 tertiles, defining non-excessive intake.

5. **Ratings of appetite** will be measured every 30 minutes between the time of ingestion of standard liquid breakfast and the start of the ad libitum meal, ratings for appetite (satiety, fullness, hunger and prospective food consumption), thirst, well-being and nausea will be recorded using visual analog scales, as described

by Flint et al. (2000). VAS, 100mm in length with words anchored at each end expressing the most positive and the most negative rating, will be used to assess hunger, satiety, fullness, prospective food consumption, desire to eat something fatty, salty, sweet or savory, and the palatability (5 questions) of the test meal. Overall appetite score will be calculated as average of the 4 individual scores (satiety + fullness + (100-prospective food consumption) + (100-hunger))/4

6. **Plasma gastrointestinal hormones (GLP-1 and PYY)** by radioimmunoassay, measured fasting, and 15, 45, and 90 minutes postprandially, with the primary endpoint being the peak postprandial level. Ghrelin and CCK levels will not be measured in proposal, since they were non-informative in our prior study.

GLP-1 will be measured as the biologically active GLP-1 (active and total) using a 2-site non-competitive immunoassay based on enzyme-labeled quantification of GLP-1 detected by a fluorogenic substrate.

PYY will be measured by radioimmunoassay (Linco Research, Inc., St. Charles, MO). PYY exists in at least 2 molecular forms, 1-36 and 3-36, both of which are physiologically active and are detected by the assay.

7. **Self-administered questionnaires** assessing affect, exercise performance, attitudes, satisfaction with body image, and eating behavior (Bush et al. 1998; Clark & King 2000; Clark et al. 2008; Lloyd-Richardson et al. 2000; Yanovski 1993; Zigmond & Snaith 1983); details of each questionnaire are provided above.

8. **Storage of biological samples:**

a. Blood Samples (fasting and postprandial) will be stored in a -70°C freezer in our lab for future assays.

b. Genomic DNA will be isolated from peripheral blood leukocytes as in previous studies (Qiagen Kit) *for possible future studies*.

9. **DEXA body composition:** Total body fat, leg fat, fat percentage, and fat free mass will be measured by DEXA scanning (QDR-2000) (Jensen et al. 1995).

10. **Liver Stiffness and fat content:** We will measure the stiffness and fat content of liver non-invasively using different ultrasound equipment at **baseline, 8 weeks and 16 weeks** in participants who provide informed consent. The GE Logiq E9 and/or the Verasonics scanner will be used to for ultrasound measurements. It is beneficial to test the measurements on different ultrasound scanners to evaluate performance. We will analyze results as we study the patients. Based on the results, we may pick one scanner (either GE or Verasonics scanner) to continue the study. Regardless whether one or two scanners are used, we will keep the ultrasound study time within 30 minutes as stated in the consent form.

General Approach for Statistical Analyses

The analyses will be based on a 2-treatment stratified design to compare the effects of liraglutide and placebo on *post-treatment gastric functions, satiation, satiety, incretins, body composition and* weight loss; *in addition, the effects of liraglutide will be compared between* patients with (vs. without) the trait of interest (i.e., the strata being accelerated vs. normal GE of solids using the 10th percentile for GE of solids in health). The analyses will use a 2-way analysis of covariance (ANCOVA) model with treatment, the quantitative trait, and a treatment by quantitative trait interaction term.

The sample size is based on the feasibility to perform a 16-week therapeutic trial over 4 years, during which approximately 40 participants completed/ year. Year 5 of the proposed application will be necessary for completion of all trait analyses, and writing manuscripts.

Interim Analysis: As part of an on-going method to compare the effects of medication tested (liraglutide) and placebo, an interim analysis will be conducted when >66% of aim 1 has been reached.

Rationale for Interim Analysis:

a. To asses power of the study based on the actual coefficient of variation as measured in the actual study with >66% completed; this is because the coefficient of variation could be different from the COV used in the a priori power calculation used in development of the protocol.

b. As part of the analysis, the statisticians will also provide a comparison of the results on the primary and secondary endpoints; this assessment will be communicated to the investigators as average data (e.g. median and IQR) for the treatment GROUPS rather than individual patient data. These group data could be used for preparation of preliminary reports in the form of abstract for national meetings specifically digestive disease week to be held in May 2021 for which the deadline for abstract submission is December 1, 2020.
c. As a result of the power analysis, it is possible that the sample size may be either reduced or increased or the study could be stopped because of "futility" if there is no evidence of a trend to suggest efficacy of treatment

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