Dietary Carbohydrate Effects on GERD in Obese Veterans: Nutritional or Hormonal?

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1.0 Background

GERD, occurring in ≥ 25% of U.S. veterans, contributes substantially to health care costs as it is the most common inpatient GI discharge diagnosis and the most common indication for upper endoscopy (upper endoscopy procedures increased 54% from 2000 to 2009 in commercially insured patients).[1] GERD is also the most common outpatient diagnosis for GI disorders with > 9 million visits annually.[1] Thus, the VA spends >$177 million yearly on outpatient PPI prescriptions. Our local VA, the Tennessee Valley Health System (TVHS), has ~65,000 total patients and 19,094 (29.4%) of these patients are currently on PPIs. Furthermore, our TVHS endoscopy lab currently sees 3-4 patients weekly for GERD that is refractory to PPI treatment.

A strong relationship has been demonstrated between the increasing prevalence of GERD and the rise of obesity in the U.S. population since the 1970's.[2,4,5,12] In fact, obesity increases the number of acid reflux episodes experienced and *the percentage of time with esophageal pH < 4.0*.[6] Thus, the American Gastroenterological Association advises weight loss for obese persons with GERD.[9] Yet, weight loss trials conducted over the past decade have not consistently demonstrated improvement in GERD symptoms, medication use, or related outcomes.[10] In contrast, a recently completed structured weight loss program in obese adults showed significant decrease in the prevalence of GERD symptoms (from 37 to 15% of subjects) with a 13% (of baseline body weight) weight loss after 6 months of intervention.[13] However, the intervention was highly structured as the primary component of the diet utilized was consumption of liquid shakes as meal replacements, not wholesome healthy foods. Beyond not being a method of training individuals how to eat in a healthful manner, the long term effects of such a strategy with regard to weight loss maintenance is unclear. It is notable that most alternative weight loss strategies are associated with a high degree of weight recidivism; a recent meta-analysis revealed that long-term weight maintenance at 4-5 years after a structured weight loss program averages about 23% of initial weight loss.[14] The dietary strategy that we propose is not only a means of improving diet related behaviors with healthful foods but also does not appear to require substantial weight loss. Moreover, our preliminary data revealed resolution of GERD symptoms in 100% of subjects.

1.1 GERD Assessment: There is no one test for establishing a diagnosis of GERD either objectively or by subject report of symptoms. As initial management of GERD is provided with antisecretory drugs (PPIs and H2RAs), diagnostic testing for GERD is typically performed after initial treatment to evaluate drug treatment failures and to identify complications of GERD such as strictures or Barrett's metaplasia. In these cases, endoscopy (with or without biopsy) is the first test used, typically for patients with dysphagia or those who have not responded to twice-daily PPI.[9] The sensitivity of endoscopy as a diagnostic test is significantly reduced since drug therapy is initiated before testing. For patients who have normal findings with endoscopy, manometry is used to evaluate lower esophageal sphincter function as well as peristaltic functioning and motor disorders. Ambulatory pH monitoring is performed (while PPI therapy is withheld) to determine the frequency, severity and duration of reflux episodes. While wireless pH monitoring appears to have greater sensitivity than impedance, impedance monitoring allows evaluation of both acid and non-acid reflux events, and is conducted for a shorter period of time (24 *vs* 48 hours of monitoring). With impedance pH monitoring, a pH score (Johnson-DeMeester Score) is calculated from 6 parameters: *percent total time pH <4.0*, percent upright time pH <4.0, percent supine time pH <4.0,

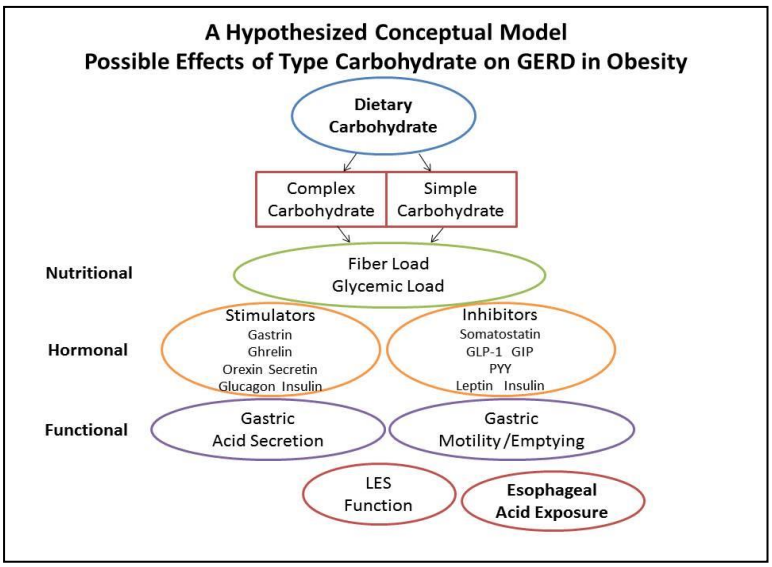
number of reflux episodes, number of reflux episodes ≥ 5min., and minutes of longest reflux episode.[15]

As GERD is a chronic disease with persistent symptoms, the importance of subjective assessment of GERD symptoms and its impact on quality of life is well-recognized. As GERD is a complex condition with many presentations, there are about 20 instruments currently used in clinical practice and/or research to evaluate GERD symptoms, typically with heartburn and regurgitation being the primary symptoms assessed. A recent systematic review showed that 5 of these 20 are evaluative scales, with the others being either diagnostic tools or epidemiologic.[16] The GERD Symptom Assessment Scale (GSAS),[17] a 15-item scale developed with patient input, is considered the most comprehensive evaluative tool as it assesses both primary and associated symptoms. The GERDQ was developed to support health care providers in diagnosing GERD as well as monitoring the response to treatment over time.[18] The GERDQ assesses frequency of symptoms and impact on life, and was based on results from a study that showed a positive correlation between the frequency of heartburn, regurgitation, sleep disturbances and use of over-the-counter medications for reflux and esophageal pH < 4.0. A randomized trial showed that the GERDQ can identify patients with a high likelihood of GERD who are in need of drug therapy as well as those who are in need of objective testing.[19]

1.2 Diet: Although avoidance of alcohol, caffeine, chocolate, acidic foods, spicy foods, mint, and high fat foods are typically recommended in treatment of GERD, there remains a lack of supporting evidence.[20-23] In fact, meta- analysis showed no efficacy for these dietary factors.[21] In contrast, a case report series and two small experiments suggest that low carbohydrate diet may improve esophageal acid exposure and symptoms. In the case series, 5 patients reported resolution of GERD symptoms within 2 weeks of following the Atkins diet which limits carbohydrate (CHO) intake to 20g per day.[24] As patients also restricted coffee, caffeine and acidic fruit intakes, it is unclear whether reduced CHO intake was the primary factor responsible for symptom resolution. Another study utilizing a crossover design with 41 subjects, compared low fat to low CHO diet for 3 months and reported that 68% of subjects had symptom improvement on low CHO diet.[25] However, the findings are subject to design bias as subjects were not randomized to treatment arm. Finally, a recent study evaluated esophageal pH in 8 obese females six days after carbohydrate restriction of 20 g/day.[26] In this study, *percent time with pH <4.0* in the distal esophagus dropped significantly from 5.1% to 2.5% (p = 0.02) and there was significant decrease in Johnson-DeMeester score from 34.7 to 14.0 (p = 0.02) – an effect similar to that expected with PPI treatment.[27] Subjects also had significant improvement in symptom severity (GSAS score from 1.28 to 0.72, p = 0.0004). Notably, the published studies utilize a severe restriction of CHO at 20g/day which confounds applicability to the VA obese adult population who typically consume ~325g/day. Furthermore, our preliminary data suggest an effect not just of amount of CHO consumed, but type of CHO. With regard to type of CHO, it is intriguing that a study in healthy volunteers reported increased number of transient LES relaxations, esophageal acid exposures, reflux episodes and GERD symptoms with administration of lactose (a simple sugar).[28]

1.3 GI Hormones and Insulin: Other studies have investigated hormones as a potential explanation for diet-induced GERD symptoms, particularly in relation to gastric motility or LES pressure. Most often studied has been the hormone gastrin, whose release is stimulated from digested food in the stomach as well as in response to gastric pH, and in

turn, is a factor influencing LES pressure postprandially.[29] Further, the orexigenic hormone ghrelin influences upper GI motility[30] and treatment with ghrelin has improved gastric emptying in rodent models.[31] Ghrelin also has a role in regulation of glucose homeostasis via modulation of insulin secretion and sensitivity.[32] Also influencing gastric emptying is the anorexigenic hormone glucagon-like peptide-1 (GLP-1), which also influences postprandial plasma glucose, insulin and c-peptide levels.[33] Finally, insulin resistance has been shown to strongly correlated with GERD symptoms,[34] an effect that is likely also related to the close correlations between obesity and GERD as well as obesity and insulin resistance. Our data, however, suggest a direct relationship because large differences in body weight were not observed. There appears to be no published evidence delineating the effects of amount or type of dietary CHO in GERD on these potential hormonal mediators. Notably, our preliminary data showed a direct relationship between type of CHO consumed, ie, simple sugar intake, and insulin sensitivity - via HOMA-IR score, an indicator of insulin resistance identified as a significant predictor of more severe GERD symptoms as well as erosive esophagitis in normal weight adults.[34]



1.4 Summary of the Problem: The VA spends >$177 million yearly on outpatient PPI prescriptions and total U.S. prescription drug spending for GERD is $10-20 billion annually. *Currently, there are 19,094 patients on PPIs at our local VA, TVHS.* However, PPIs do not prevent reflux of non-acidic material and do not completely eliminate esophageal acid exposure. Hence, GERD symptoms persist in ≥ 40% of patients treated with PPIs. Unresolved GERD leads to significant comorbidities - it appears ~25% of veterans age >50 years have Barrett's Esophagus,[35] a premalignant condition which leads to esophageal adenocarcinoma, the most rapidly rising type of tumor in the VA population. In addition, GERD increases risk for laryngeal and pharyngeal cancers in veterans.[36]

Although a strong relationship has been demonstrated between the increasing prevalence of GERD and the rise of obesity in the U.S. population since the 1970's, weight loss trials have not consistently demonstrated improvement in GERD symptoms, medication use, or related outcomes - there remains insufficient evidence for dietary recommendations for veterans with GERD.

1.5 Opportunity Presented Here: This study will rigorously test a compelling hypothesis regarding GERD pathophysiology and will provide evidence from a randomized controlled trial in this at-risk population for whom there is little evidence-based insight with regard to readily modifiable dietary risk factors. Dietary intervention has been demonstrated and is predicted to have other salutary effects such as improved body weight, insulin sensitivity and lipid profiles.

1.6 Innovation of Study: While it has long been thought that dietary factors play a role in promoting or exacerbating GERD symptoms, we are unaware of any evidence that effects of dietary macronutrients have been rigorously tested. Indeed, a PubMed search only returned 2 articles on diet and GERD in a veterans' population. The very limited body of literature has targeted dietary fat and saturated fat intake. Yet, our preliminary data show a strong relationship between dietary simple carbohydrate (sugars) and GERD. In fact, our data show that obese subjects with GERD had complete resolution of their symptoms and medication use when following a low carbohydrate diet in which simple carbohydrate intake was strictly controlled. Obese individuals with GERD have rarely been studied beyond investigation of an association between body mass and GERD symptoms or between dietary fat intake and GERD symptoms. Our proposal to investigate the role of dietary carbohydrate is unique and the robustness of the proposed experimental design is novel in the GERD literature. Indeed a PUBMED search of carbohydrate and gastroesophageal reflux returned only a single citation; "Improvement of gastroesophageal reflux disease after initiation of a low-carbohydrate diet: five brief case reports" Altern Ther Health Med. 2001 Nov-Dec;7(6):120, 116-9.

A lifestyle intervention that is novel in terms of GERD thinking, efficacious at improving insulin sensitivity, and that is likely to beneficially effect other common obesity co-morbidities would represent a highly innovative approach to controlling GERD in the obese Veteran population.

1.7 IMPACT: PPIs are one of the top 5 highest selling pharmaceuticals; the VA spends >$177 million yearly on outpatient PPI prescriptions and total U.S. prescription drug spending for GERD is $10-20 billion annually. Yet, ≥ 40% of individuals on PPIs or H_2RAs fail to respond. *Our local VA, the Tennessee Valley Health System (TVHS), has 19,094 patients on PPIs currently.* Aside from quality of life, GERD is a substantial source of morbidity, leading to esophagitis, strictures, Barrett's esophagus and esophageal adenocarcinoma. The incidence of GERD and esophageal adenocarcinoma has increased >350% since the mid-1970's, which parallels the increased prevalence of obesity during the past 3-4 decades. In addition, obesity is associated with a 2.5-fold increased risk of Barrett's esophagus in veterans.[37] The proposed dietary intervention, if deemed efficacious, can be directly implemented in daily clinical practice – without high costs or adverse side effects. It offers the potential to reduce symptom burden and medication use, and will provide evidence needed for future investigation of long-term sequellae of GERD. As 72% of the VA population is now overweight or obese,[7,8] and at least 25% currently have GERD, we will generate significant information regarding a serious pathophysiology that not only fills a gap in the evidence base where only case reports exist, but will inform clinical practice and has potential to reduce health costs.

2.0 Rationale and Specific Aims

General Approach: We will use a randomized controlled trial design to rigorously test the hypotheses that low total carbohydrate and/or low simple (low sugars) carbohydrate dietary intake will reduce/resolve GERD in obese veterans. From our preliminary data of 144 obese adults, we found that total carbohydrate was comprised of ~ 50% complex CHO and ~50% simple CHO (sugars) - prior to dietary intervention. Thus, that composition forms the definition for our control diet (below).

2.1 Rationale and Strategy:

Background PPI Use: Acid suppression therapy is commonly prescribed, particularly in the VA for symptomatic GERD relief. Our research team, which includes practicing clinicians and experienced GERD researchers (Drs. Vaezi and Smalley) debated a design wherein we would require research subjects to discontinue all acid suppression therapy for the duration of the study. It is clear that based upon symptom burden and for the purposes of adherence to study procedure that this would not be feasible. Further, we were concerned that if acid related damage were occurring off of acid suppression, then such a design may not be ethical. Thus, we have adapted a much more "clinical" or "intention-to-treat" mindset to the study design. Indeed, in a clinical setting, patients are most often treated empirically. Thus, we will follow AGA guidelines[9] and have subjects maintain acid suppression therapy during the intervention, with the exception of the 7-day period prior to impedance and manometry testing. To determine the effect of acid suppression on the hormonal milieu we will now draw blood pre and post medication discontinuation. The only potential confounder to this approach would be if the efficacy of the dietary intervention were dependent upon having a highly acid and refluxing esophageal environment. This does not seem biologically plausible, and additionally the efficacy of the dietary intervention to reduce GERD in our preliminary data was not acid dependent given that all subjects self-discontinued use of acid suppression medications. *We will perform secondary analysis in which changes in PPI use over time will be assessed. We will use the daily medication (type and dose) and diet checklist data and 24hr diet recall data to conduct secondary analyses and verify the assumptions of our primary model. Summary statistics by diet group will be calculated to determine if weight loss, PPI use, total CHO, and simple CHO are consistent with the study design. We will also use the linear mixed effects model to determine if total and simple CHO are associated with total percent time pH < 4 by replacing the indicator variables in the primary model with these continuous covariates and their interaction. A secondary analysis of changes in PPI use over time will be considered. For this analysis, we will use the daily medication checklist (type, amount and dose) to create continuous variables of the weekly dose of PPI. PPI dose will be the outcome in a linear mixed effects regression model that includes time modeled flexibly using restricted and diet group indicators. An analogous model using weight as the outcome will be estimated.*

Choice of Objective Disease Measures: As described above in section 1.1, we will employ impedance pH monitoring to determine acid and non-acid reflux events over a 24-hour period. This will allow data collection for *our primary outcome, percent of time with pH < 4.0*, as well as the other 5 measures that comprise the Johnson-DeMeester score.[15] For motility, we will use the the SmartPill monitoring system, which measures whole and regional gut transit times. Kuo et al[38]and Sarosiek et al[39] describe sensitivity and specificity for the SmartPill. SmartPill gastric emptying time was compared to gastric emptying scintigraphy (GES). Correlation between SmartPill and GES was 0.73, the

ROC curves between healthy subjects and gastroparetics was 0.83 for SmartPill and 0.82 for GES, and the sensitivity/specificity for diagnosing gastroparetics for SmartPill was 0.65 / 0.87 and for GES was 0.44 / 0.93. In addition, Maqbool et al[40] showed correlation between SmartPill transit time and scintigraphy was 0.95 at 120 mins and 0.73 at 240 mins. Finally, Timm et al[41] showed SmartPill assesses transit time in a within-subjects dietary crossover trial, where the amount of food was controlled but fiber source differed, indicating reliability for assessing dietary carbohydrate changes. Delayed gastric emptying is implicated in such disorders as idiopathic and diabetic gastroparesis and functional non-ulcer dyspepsia. The primary outcome measure from this test will be gastric emptying time. We recognize that a possible limitation of our proposed study is that we are not performing endoscopy to determine mucosal damage. While we will are using the clinical gold standard assessment of pH and reflux, it is well beyond the scope and capacity in this study to perform endoscopic assessments of mucosal health. Demonstration of a strong effect of the dietary intervention on GERD could prompt the development of future more invasive studies to examine such effects.

Choice of Subjective Disease Measures: As there are ~20 instruments to assess GERD symptoms, most of which were evaluated in a systematic review,[16] we have chosen two scales, the GSAS[17] and the GERDQ,[18] that have strong sensitivity and also have both item and context validity (both are more fully discussed above in section A.1., and in the Measures section i below).

Duration of Intervention: Implementing a dietary intervention can present some challenges with regard to dietary compliance as well as subject retention for the duration of a study. Our preliminary data shows a significant effect of low carbohydrate diet after 9 weeks of intervention – all subjects with GERD had resolution of their symptoms and GERD medication use. In the proposed study, we have chosen to continue to use a 9-week intervention period as we would expect that obese adults may find it difficult to adhere to a longer term dietary change and this study is not designed to investigate behavioral issues. Attrition would be problematic as it may statistically underpower the study or bias the results and negatively affect internal validity of the study. Our aim is to minimize potential attrition, maximize statistical power, and minimize the time commitment while providing a dietary intervention of adequate duration to experience effects.

Weight Loss: We recognize the benefits of weight loss in the obese veteran and are highly encouraged by the enormous resources dedicated to the MOVE! program. Interestingly, our preliminary data showed resolution of GERD symptoms and medication use, as well as improvement in insulin sensitivity – independent of weight loss. To clearly determine the effects of the modifying dietary carbohydrate intake *per se* and control for potential confounding (which would distort study findings) by changes in body weight during the course of the study, subjects will be prescribed diets in which the energy content will maintain body weight, not induce weight loss. Body weight will be monitored by the study dietitian. Body composition will be assessed at end of study weeks 1 and 9 by use of DEXA (described in Measures section below). Upon completion, the study dietitian will counsel subjects about unhealthy weight and provide a written handout on caloric reduction for weight loss.

2.2 Methods:

Design: Randomized controlled dietary trial with 4 treatment arms comparing amount and type of CHO:

- High total & high simple carbohydrate (HTHS): 50% complex CHO + 50% simple CHO (control diet)
- High total & low simple carbohydrate (HTLS): 85% complex CHO + 15% simple CHO
- Low total & high simple carbohydrate (LTHS): 50% complex CHO + 50% simple CHO
- Low total & low simple carbohydrate (LTLS): 85% complex CHO + 15% simple CHO

Diets: We have extensive experience designing, prescribing and assessing diets.[42,43] At baseline, dietary intake will be assessed by the Vanderbilt Nutrition and Diet Assessment Core (full methods described under Measures below). Energy content of daily intake will be estimated based on the individual's daily energy requirement using the Harris Benedict Equation with an activity factor of 1.2.[44] By doing so, calorie level will be individualized to assure weight maintenance during the study. In addition to being weighed at each clinical testing visit, body composition will be evaluated via DEXA scans at clinical testing visit to assure no changes in either total fat or truncal fat mass influence study results.

Subjects will be provided with daily meal plans that adhere to the composition of the treatment arm to which the subject is randomized. Meal plans will be developed by the co-Investigator (Silver) using NDS-R software (NDS-R version 2013, Nutrition Coordinating Center, Minn, MN) and instructed to subjects by the study dietitian at the end of study week 1 (see Schema below). To manipulate the carbohydrate amount (high *vs* low), we will alter the fat content of the diet. There will be no difference among diets in protein content. To manipulate type of carbohydrate (complex *vs* simple), we will provide instructions, the written meal plan, and a comprehensive list of which carbohydrate foods the subject can/can't consume.

To clearly delineate, simple carbohydrates are defined as those carbohydrates classified as mono- or di-saccharides, meaning they have one (glucose, galactose, fructose) or two (sucrose, lactose, maltose, trehalose) sugar units. Major sources of simple carbohydrates (or "sugars") are: soft drinks, cakes, cookies, pies, fruit punch, sweet tea, candy, table sugar, and syrups. Complex carbohydrates are also known as "starches" and consist of the oligo- and poly-saccharides, meaning they have 3 or more sugar units. Major sources of complex carbohydrates (or "starches") are: grains, cereals, legumes, corn, popcorn, pasta, rice, potatoes and vegetables. We recognize that major sources of both simple and complex carbohydrates have components of both and we are able to quantify these within a food using the NDS-R software.
All meal plans will provide 3 meals and 2 snacks per day that meet the macronutrient composition and the diet treatment arm:

- HTHS Diet: 55% total CHO (½ complex / ½ simple CHO), 30% fat, 15% protein
- HTLS Diet: 55% total CHO (85% complex / 15% simple CHO), 30% fat, 15% protein
- LTHS Diet: 35% total CHO (½ complex / ½ simple CHO), 50% fat, 15% protein
- LTLS Diet: 35% total CHO (85% complex / 15% simple CHO), 50% fat, 15% protein

Power Analysis and Sample Size: *Our primary outcome is a continuous variable, percent time pH < 4.0 in the 24hr period. This is based on the clinical gold standard of pH < 4.0 for > 5.5% of the 24hr period. To determine sample size, we used data from 205 obese patients with chronic GERD from Dr. Vaezi's clinic population. In this sample, the SD for percent time < pH was 9.8 and the interclass correlation was 0.39 (□ = $□^2_b$ / ($□^2_b$ + $□^2_e$)). We used these values as inputs into a statistical simulation (10,000 replications) to determine the probability of detecting any treatment group effect using the linear mixed effects model. The following table presents the power of an overall (4 d.f.) test to detect various absolute changes in pH by diet groups (□1, □2, □3, □4). We assume n_1=40 subjects per group complete the entire study and n_2=5 or n_2=3 subjects per group complete 80% of the study before returning for pH testing. We use a two-sided significance level of 0.05.*

Absolute effect size	*3.7%, 3.7%, 3.7%, 3.7%*	*0%, 4.5%, 4.5%, 4.5%*	*0%, 4%, 4%, 4%*	*0%, 0%, 5%, 5%*	*0%, 0%, 0%, 7%*
Power (n_1=40, n_2=5)	*0.80*	*0.89*	*0.80*	*0.85*	*0.87*
Power (n_1=40, n_2=3)	*0.79*	*0.88*	*0.79*	*0.83*	*0.86*

Power for different effect size scenarios that give 80%-90% power are presented in the table. If the absolute change in percent time pH < 4 for each of the four diet groups is 3.7%, we will have 80% power to detect any effect of diet. If 1 diet group is not effective and the other groups have a 4.5% effect, we have almost 90% power to detect a diet effect. In our pilot data, the 25th/50th/75th percentiles of percent time pH < 4 were 4.8%/8.5%/12.4%. Thus, a 3.7% decrease is a change from the median to 25th percentile, a 4% decrease is a change from the 75th percentile to the median, a 5% decrease is a change from the 80th percentile to the median, and a 7.6% decrease is a change from the 75th to the 25th percentile. The standard error for any pairwise comparison between groups will be 1.9% under all scenarios (n_1=40 and n_2=3 or n_2=5).

2.3 SPECIFIC AIMS:

Gastro-esophageal reflux disease (GERD) occurs in 25-30% of U.S. adults, including veterans,[1] and the prevalence of GERD is increasing.[2,3] GERD is the most common inpatient gastrointestinal (GI) disease discharge diagnosis and the most common outpatient diagnosis for GI disorders in the U.S. with > 9 million visits annually.[1] The VA spends >$177 million yearly on outpatient prescriptions for GERD. Higher body mass index (BMI) is associated with increased risk for GERD,[4-6] and the increasing prevalence of GERD is likely related to the obesity epidemic.[2] Indeed, 72% of veterans are overweight or obese.[7,8] The odds ratio of having GERD is 3-fold greater for obese men and 4-fold greater for obese women (compared to normal weight adults). Thus, the American Gastroenterology Association guidelines advise weight loss for overweight/obese people with GERD.[9]

It has long been thought that several dietary factors (acidic foods, spicy foods, mint, chocolate, caffeine and alcohol) as well as a high fat diet may precipitate GERD symptoms. In fact, most studies on dietary factors have targeted total and saturated fat intake as risk factors. However, most of the evidence comes from epidemiological data or clinical data from hospitalized patients with the most severe forms of GERD (esophagitis and adenocarcinoma). When data are adjusted for BMI the relationships between total or saturated fat intake and GERD are not significant. Furthermore, weight loss trials utilizing low fat diets have not consistently demonstrated improvement in GERD symptoms.[10]

We recently conducted a nutrition intervention utilizing a low carbohydrate / high fat diet in 144 Caucasian and African American adults age 21-50 years with Class I obesity (BMI 30.0-39.9). At baseline, 25% of subjects reported experiencing GERD symptoms (heartburn, reflux and/or indigestion) at least once a week. Over 1/3 used a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H_2RA) at least once a week. At baseline, we found that subjects with GERD had significantly higher total sugar intakes (101.6 ± 50.3 *vs* 82.5 ± 40.9 grams/day, p = 0.024), but not higher total fat intakes. Notably, total sugar intake was a strong predictor of having GERD symptoms (p = 0.007). *Most unexpectedly, all GERD symptoms and medication use had resolved by completion of the 9-week low carbohydrate / high fat diet intervention.* Moreover, reduced total sugar intake was significantly associated with improved insulin sensitivity (HOMA-IR score: r =0.37, p =0.001), independent of weight loss.

Overarching Hypothesis: Our overarching hypothesis is that the type (not just the amount) of dietary carbohydrate intake contributes to GERD symptoms in obese persons.

Specific Hypothesis: Our preliminary findings suggest a physiological mechanism between dietary intake and GERD that may be related to type of dietary carbohydrate intake (complex *vs* simple carbohydrate). We hypothesize that modifying the type of dietary carbohydrate consumed - by reducing the proportion of simple carbohydrate (sugars) consumed - will reduce or resolve GERD symptoms and medication use in obese veterans with chronic GERD. We further hypothesize that the mechanistic effects of reducing simple carbohydrate intake is related to either: a) improved dietary fiber intake and/or glycemic load, and thus, reduced amount and duration of esophageal acid exposure; and/or b) improved insulin sensitivity which would positively influence the function of key gastrointestinal hormones (ie, gastrin, glucagon, GLP-1, ghrelin[11]) that regulate gastric motility and/or lower esophageal sphincter function.

Aim 1: *To determine effects of dietary carbohydrate consumed (amount and type) on percent time with esophageal pH < 4.0, as well as number of reflux episodes, GERD symptoms and GERD medication use, in 200 obese veterans* who have chronic high frequency of GERD symptoms. To meet this aim we will use a randomized controlled trial in which we manipulate amount of total and simple dietary carbohydrate intake for duration of 9 weeks.

Aim 2: To assess associations between GERD resolution variables and factors related to potential mechanisms by which modifying dietary carbohydrate intake could resolve/reduce GERD in obese veterans.

2a: We will investigate associations related to whether the effect is nutritionally mediated by measuring change in dietary fiber load and dietary glycemic load, and thus, whether these changes are related to improved gastric acid secretion (*% time pH < 4)*, gastric motility, and/or the other parameters that comprise the Johnson-DeMeester score.

2b: We will also investigate whether effects are associated with changes in the hormonal milieu by measuring hormonal response of gastrin, glucagon, GLP-1, ghrelin and insulin, which could potentially influence gastric acid secretion, gastric motility and/or lower esophageal sphincter function.

3.0 Animal Studies and Previous Human Studies

PRELIMINARY DATA

In a recently completed study designed to investigate the effects of a high fat diet on cardiometabolic outcomes in 144 obese adults (Silver and Niswender), we found that 36 of 144 (25%) had a history of GERD symptoms and/or medication use at least once a week at baseline.

Closer assessment of subjects' dietary intakes revealed that subjects with GERD had significantly higher energy intakes, simple carbohydrate intakes (total sugar), sucrose intakes, and overall dietary glycemic load – but not higher dietary fat or protein intakes (Table 1). In addition, there was no difference in subjects' intakes of caffeine, as well as alcohol, chocolate or other dietary factors commonly associated with GERD (data not shown). Notably, in regression modeling, total sugar intake was a strong predictor of having GERD symptoms (p = 0.007).

Table 1. Baseline Demographic and Nutrient Differences

	GERD (N = 36)	No GERD (N = 108)	*P*-Value
Demographics			
Age (y)	39.2 ± 5.9	35.9 ± 6.9	**0.011**
Race			**0.039**
Caucasian	30 (83%)	70 (65%)	
African American	6 (17%)	38 (35%)	
Nutrients (per day)			
Amount of Food (g)	2675.7 ± 610.1	2778.1 ± 815.9	0.491
Energy (kcal)	2103.1 ± 435.2	1840.1 ± 435.0	**0.002**
Fat (% kcal)	37.2 ± 6.0	38.7 ± 7.8	0.311
Protein (% kcal)	15.6 ± 2.9	16.9 ± 4.6	0.095
Carbohydrate (% kcal)	46.5 ± 6.1	43.9 ± 9.6	0.135
Total Fiber (g)	16.8 ± 6.5	15.2 ± 5.8	0.177
Soluble Fiber (g)	5.9 ± 2.8	5.0 ± 2.1	**0.037**
Total Sugar (g)	101.6 ± 50.3	82.5 ± 40.9	**0.024**
Sucrose (g)	52.8 ± 37.8	36.6 ± 23.5	**0.003**
Fructose (g)	16.3 ± 12.6	16.8 ± 12.1	0.821
Glycemic Load	198.9 ± 51.4	166.2 ± 59.1	**0.004**
Caffeine (mg)	160.1 ± 112.6	133.7 ± 102.6	0.195
HOMA-IR (score)	2.9 ± 2.5	2.5 ± 2.0	0.278

In the subjects with GERD, all GERD symptoms and medication use had resolved by completion of the 9-week low carbohydrate / high fat diet intervention. While there was no difference in the average amount of food consumed per day between subjects with GERD versus those without, the subjects with GERD did have significantly greater reductions in energy intakes, sucrose intakes, and overall dietary glycemic load (Table 2).

Table 2. At Week 9 of Low Carbohydrate / High Fat Diet			
	GERD	**No GERD**	
Baseline GERD Status	N = 36	N = 108	
GERD Resolved	**36/36**	n/a	***P*-Value**
Amount of Food (grams)	-141.8 ± 573.7	-179.2 ± 775.5	0.821
Energy (kcal)	-372.7 ± 400.1	-144.7 ± 425.4	**0.018**
Fat (% kcal)	12.9 ± 6.3	10.9 ± 8.2	0.239
Protein (% kcal)	4.8 ± 3.7	4.5 ± 4.5	0.792
Carbohydrate (% kcal)	-17.5 ± 6.2	-15.3 ± 8.9	0.241
Total Fiber (g)	3.3 ± 8.4	5.2 ± 5.7	0.211
Soluble Fiber (g)	2.5 ± 2.9	3.6 ± 2.7	0.114
Total Sugar (g)	-62.1 ± 44.0	-43.4 ± 42.1	0.057
Sucrose (g)	-37.5 ± 28.2	-22.3 ± 25.4	**0.013**
Fructose (g)	-9.6 ± 12.8	-8.6 ± 10.9	0.711
Glycemic Load	82.5 ± 30.1	62.2 ± 39.9	**0.018**
Caffeine (mg)	117.2 ± 92.9	101.9 ± 106.8	0.513
HOMA-IR Score	-1.1 ± 1.8	-0.3 ± 1.2	**0.018**

4.0 Inclusion/Exclusion Criteria

As race, age and gender have not been shown to affect GERD status, we will enroll any interested patient who meets the following criteria:

Inclusion Criteria	Exclusion Criteria
• Age: ≥ 21 years • *BMI: 25-45 kg/m^2* • *GERD diagnosis in the medical record which will be confirmed by study baseline pH testing, if baseline pH is not < 4.0 for ≥ 5.5% of time during 24hr testing, subject will be excluded.*	• History of type 1 diabetes • Hernia > 5 cm • Current or remote history of esophageal stricture • Gastroparesis • Extra-esophageal GERD • Barrett's esophagus or Esophageal adenocarcinoma • History of gastric or bariatric or esophageal surgery, radiation or cancer • History of gastrointestinal malabsorption • *Alcohol averaging > 2 drinks per day during past 3 months* • Pregnancy / Lactation

5.0 Screening & Enrollment

All recruitment procedures will be IRB-approved. Study participants will be recruited from the VA clinic patient population under the guidance of Dr. Walter Smalley, study co-investigator and VA gastroenterologist. We anticipate that the majority of patients will be recruited from primary care clinics. We will also engage the VA pharmacy service, utilizing the robust electronic medical record system, to identify patients currently on prescriptions for GERD and who have relevant diagnoses (i.e., ICD-9 codes 530.81 and 530.11) and are scheduled to come to a given clinic on a specific day. Our study nurse will work closely with charge nurses and clinic staff to identify potential subjects. Upon review of pharmaco-economic data from TVHS, we have identified that 45% of the total TVHS veteran population of 65,000 are obese and that there are currently 19,094 patients on PPIs. In the course of clinic interactions, clinic staff will determine whether a patient has general interest in participating in this study (i.e., provides verbal consent to be approached by study nurse for full description of study procedures). From our more intensive GI clinical trials, we currently enroll 30-35% of patients approached (personal communication W. Smalley).

Based upon prior published studies in VA facilities, successful recruitment for patients with GERD has been documented from the following clinical settings: internal medicine/primary care clinics, emergency department, and lastly, general GI clinics. We will initially focus our recruiting efforts on the Nashville campus, the Charlotte Avenue primary care clinic facility, and at the Murfreesboro Alvin York campus, as a high volume of primary and specialty care occurs at these three sites.

A secondary recruitment strategy will involve the placement of IRB approved posters and brochures in the waiting areas of target clinics with basic study information and a contact line for potential subjects to register potential interest. We anticipate screening 6-10 subjects per week for eligibility. We will perform a baseline pH study after consent. Based on clinical experience, we expect 15-20% of Vets diagnosed with GERD will be screen failures as they will not have pH < 4.0 for > 5.5% of a 24-hour period (personal communications W Smalley & M Vaezi). These 15-20% will be excluded from study as the underlying hypothesis is that low carbohydrate / low sugar diet will reduce % time with pH < 4.0 to < 5.5%. Thus, we expect to meet our targeted enrollment of 1-2 subjects per week, which is based on the ability to schedule this number of patients in the GI clinic for pH testing. Thus, our recruitment and enrollment goals appear to be highly feasible with such a huge patient population at TVHS (currently a total of 65,000 patients; 29,250 of whom are obese, and 19,100 are currently on PPIs, thus ~65% of these obese vets have GERD).

6.0 Study Procedures

Randomization: *200 subjects (50 per arm) will be randomized to diet treatment arm. we have reviewed drop-out rate from clinical trials in gastroenterology in this population (W. Smalley and M. Vaezi personal communications), which would predict a 20% drop out rate. The number of subjects to enroll reflects a completion rate of 80% (enroll 50 per arm = 200 subjects x 0.80 = 160 completers). In considering that drop out could be higher, we will now include subjects in our final analyses who notify us they are dropping-out between weeks 7–9 by asking them to return for a final visit at the time of drop-out (we do this regularly and get agreement from about 66% of subjects to return for a final testing session even if they are not continuing to wk 9).* Randomization of subjects will be carried out using unified reproducible methods (i.e. saved random number seed) provided by the Biostatistician (Slaughter). We will use a permuted block randomization scheme, stratifying on gender to ensure this covariate is balanced

between randomization groups. The block size will be varied randomly. Treatment assignments will be contained in sealed, thick envelopes to be opened after informed consent is obtained.

Overall Schema:

Timepoint	Baseline	Day 1-7	End Wk 1	Day 8-57	Day 57-63	End Wk 9
Consent & Enrollment	X					
Randomization			X			
Bloodwork	***X***		***X***		***X***	***X***
Diet Intervention						
Off PPIs #1						
Clinical Testing #1			X			
Off PPIs #2						
Clinical Testing #2						X

Testing Procedures:

Baseline levels of all measures listed below will be obtained prior to study day 1.

PPIs will be stopped for 1 week, medications that affect gastric motility for 2 days, H_2RAs for 2 days, and antacids for 2 days - *prior to testing on study days 7 and 63. Additional blood work will be drawn on study day 57 for evaluation of levels prior to discontinuation of PPIs #2.*

Subjects will be instructed to stop eating and drinking, except water, at 10pm on the evening before each clinical testing day. Thus, subjects will arrive at the VA on study days 7 and 63 NPO. Subjects will be escorted by study staff from the VA to the Vanderbilt Clinical Research Center at 0700. Subjects will be admitted to a private outpatient room (has private bed and bathroom). An updated medical history will be obtained to ensure absence of recent/current illness. CRC nursing will obtain vital signs and perform the blood draw. As part of the blood draw, female subjects will have a pregnancy test (via serum βHCG). The study dietitian will perform anthropometric, body composition (DEXA), dietary and GERD symptom survey measures as described below. The subject will then be escorted by study nurse to the Vanderbilt GI Clinic for impedance monitoring and gastric emptying test procedures under the guidance of Dr. Michael Vaezi (study co-investigator), as described below. Impedance monitoring will continue for a 24-hour period. Subjects will be provided with a meal that is consistent with the diet intervention and the treatment arm they are assigned to before being discharged home. The study nurse will telephone subjects in the early evening to assure no problems from study procedures have developed. Subjects will return to the VA to meet briefly with the study nurse on the day after clinical testing to allow data retrieval and return of impedance monitoring and gastric emptying equipment.

For these Testing Visits, at the end of study week 1 and study week 9, participants have the choice of staying overnight in a private room at the Vanderbilt Clincial Research Center for the 24-hour period of testing, or they can return to the Vanderbilt Digestive Disease clinic on the morning after the 24-hours of pH and SmartPill monitoring for the removal of the pH catheter and collection of the recording devices.

Measures: to be performed in the fasting state at baseline, end study week 1, pre/post study week 9

- **Bloodwork:**
  - **Glucose:** Plasma glucose concentration will be analyzed in triplicate via glucose oxidase method using a Beckman glucose analyzer at the VA Clinical Laboratory.
  - **Insulin:** Plasma insulin concentration will be shipped to LabCorp and analyzed by radioimmunoassay method**.**
  - **HOMA-IR:** Calculated from glucose and insulin values.
  - **Hormones:** Serum gastrin will be assayed at LabCorp. Glucagon and GLP-1 by Luminex multiplex assay at the Diabetes Hormone core lab. Serum ghrelin (active acylated form) by radioimmunoassay at the Diabetes Hormone core lab. While several other hormones are involved in gastric acid secretion and motility, we have chosen two key stimulators (gastrin and glucagon) and two key inhibitors (GLP-1 and ghrelin), as well as insulin, to investigate in this proposal utilizing a dietary intervention in obesity.

- **Anthropometrics:**
  - **Height** (m) and **Weight** (kg) measured on calibrated digital equipment will be used to calculate **BMI**.
  - **Waist Circumference"** will be measured using a flexible tape at the level of the umbilicus.[45]

- **Body Composition:** In addition to total and regional body composition (fat, lean and bone mass) obtained from the Lunar iDXA (GE Healthcare), we will use new technology recently acquired by VICTR to estimate visceral adipose tissue (VAT) – a possible risk factor for GERD.[46] This fully automated approach to capture VAT has been validated against CT[47] and offers several advantages to MRI or CT: fast, low cost, exposes one to less radiation, and makes serial measurements possible.

- **Metabolic Testing: To capture a more objective measure of change in energy balance due to the dietary intervention, we will perform indirect calorimetry by metabolic cart while subjects are at the CRC on week 1 and 9.**

- **24 hour urine collection:** To effectively measure how well the body processes food intake

- **Dietary Intake:** will be assessed via averaging three 24-hour diet recalls obtained at baseline and again within a 7-day window of each clinical testing visit (study weeks 1 and 9). Recalls will be performed by the Vanderbilt Nutrition and Diet Assessment Core using the USDA multi-pass methodology,[48,49] a standardized script, and computer-generated prompts (NDS-R, v. 2013, Nutrition Coordinating Center, Minn, MN). We are familiar with underreporting especially in people with high BMI and use portion size tools and statistical methods to assure

data reliability. The 1st of 3 recalls will be in-person at the CRC, which allows training of subjects in the interview methodology.

- ***Medication Use:*** *will be assessed by two methods: a) we will provide subjects with a notebook that includes daily logs for them to record medication type and amount; and b) weekly interview by study nurse. In addition, we now have bloodwork being drawn pre and post weeks 1 and 9 that will inform medication use by measurement of hormone levels, i.e., gastrin.*

- **24-Hour Impedance Monitoring:** will be performed by using a combined MII-pH monitoring device (Sandhill Scientific Inc; Highlands Ranch, CO) comprising a data recorder (Sleuth System; Sandhill Scientific Inc) and a 2.1 mm diameter polyvinyl catheter embedded by one pH and 6 impedance sensors at predefined positions. The pH sensors are calibrated before placement using standardized buffer solutions at pH 4.0 and 7.0 per manufacturer. The catheter is placed intranasally so that the esophageal pH sensor is positioned 5-cm above the manometrically defined upper border of the lower esophageal sphincter (LES). Intraluminal impedance is measured at 3, 5, 7, 9, 15 and 17cm above the LES. Data sampling frequency for both impedance and pH sensors is 50 Hz. Data are downloaded from the recorder and analyzed using BioView Analysis software (Sandhill Scientific Inc). Reflux episodes are identified by computerized detection (Autoscan; Sandhill Scientific Inc.) of proximally directed decreases in impedance. Tracings are also manually reviewed by an experienced investigator (Vaezi) to confirm accuracy and correct errors. Total, upright and supine reflux events are recorded. Acid reflux events are defined as those with pH ≤ 4 and non- or weakly acid reflux events are those occurring at pH > 4.

- **Gastric Emptying:** Subjects will swallow an activated and calibrated SmartPill wireless pH, pressure and temperature capsule. The capsule houses sensors for pH, temperature and pressure. Shape and dimensions of the capsule are: cylindrical, 26.8mm long by 11.7mm in diameter. The capsule has a pH range of 0.5–9 with an accuracy of ± 0.5 pH units. The pressure sensor has a pressure range of 0–350 mmHg with an accuracy of 5 mmHg below 100 mmHg and 10% at or above 100 mmHg. The temperature sensor has a range of 25–49 C, with an accuracy of ± 1 C. Subjects ingest the capsule with 50 cm^3 of water and afterwards begin eating a standard meal with an additional 120 cm^3 of water. After activation and ingestion, the capsule signals are transmitted from within the GI tract and are captured by a receiving antenna incorporated into the receiver. The portable receiver worn by the subject receives and stores data which is downloaded to a PC computer. The transfer of data to the PC is accomplished via placement of the receiver in a docking station which provides an interface for data transmission to a computer as well as connections for battery charging. MotiliGI software (SmartPill, Inc.) loaded on the computer supports the data transfer, analysis of the recorded date, and displays the test results. Capsule gastric emptying time is defined as the duration of time from capsule ingestion to an abrupt pH rise (usually >3 pH units) from gastric baseline to a pH >4 as the capsule passes from the acidic antrum to the more alkaline duodenum.

- **GERD Symptoms:**

- **GERD Symptom Assessment Scale (GSAS)** will be used to measure the frequency, severity and distress for GERD symptoms. Internal consistency is >0.80 for symptom severity and distress scales. Validity, stability and sensitivity to change in symptom severity over time have been confirmed.[17,50]
- **GERDQ** is a 6-item self-administered questionnaire designed for diagnosis and management of the GERD patient. It differentiates patients with occasional reflux symptoms from those with frequent symptoms. Two items measure impact of GERD symptoms on daily life and 4 items are used to monitor and evaluate the impact of treatment over time.[18]

7.0 Risks

- Following a special diet and keeping a record of what is eaten and medication use may be inconvenient to participant.
- The participant will be required not to eat or drink, except water, after 10 pm on the night before testing visits at the end of study weeks 1 and 9. This may cause the participant to have a headache or a feeling of weakness, or the participant may become irritable.
- Blood draw: Blood draws can cause redness, soreness, bleeding or bruising at the needle stick site. The CRC nurses will be careful and use sterile technique. Sometimes people feel faint. The nurse may put some cream (called EMLA) on the skin to numb the area so the participant will not feel the needle stick as much. The numbing cream may make the skin change color, but this is rare.
- DEXA: Because DEXA is an x-ray, the participants are exposed to some radiation. The amount of radiation from the 2 DEXA scans is equal to the amount of radiation in the natural environment if the participants were to walk around outside for 17 days.
- Because the participant will not be taking medication for GERD while are participating in this study, it is possible that GERD symptoms may get worse.
- 24-hour pH Monitoring:
  - Lidocaine: Lidocaine, a numbing drug, has an awful taste and causes a strange feeling in the mouth. There is a rare side effect that this drug may cause hoarseness and loss of voice. There is a very rare risk that this drug may cause problems with heart rhythm.
  - Possible risks for the participants during 24-hour study include: nasal discomfort, injury to nasal passages such as nose bleedings, allergic reaction to lidocaine gel used to numb the nasal passages for placement of tube, and rupture of the esophagus by the long tube which may require an operation.
    - Smart Pill: You may experience discomfort when swallowing the smart pill. In rare cases, the smart pill could get lodged or stuck in your esophagus. This may require a procedure to remove the pill. If you have an abnormality in how your esophagus works this may increase the risk.

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Risks that are not known:
There are no known risks with any of the 4 diets. If new information is discovered that may affect the risks or benefits of this study, the participant will be told so that he/she can decide whether or not to remain in the study.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

All serious and unanticipated adverse events or problems involving risks to subjects that may possibly be or are known to be related to the research activity will be reported promptly to the IRB office per Vanderbilt University IRB Policy. The PI will ensure proper data and safety monitoring for the materials and data used for the purposes of this study.

9.0 Study Withdrawal/Discontinuation

Subjects may choose not to participate in this research study. This decision will not alter the routine care administered by the physician or the risks associated with standard of care procedures. Additionally, the participant will be removed from this study if the investigator does not think it is in best interest for the subject to be in this study. If the participant is removed from the study he/she will be told the reason why.

10.0 Statistical Considerations

Data Analysis: To determine *if percent time with pH < 4 differs by diet treatment group*, we will use multivariable linear regression modeling. Models will include baseline percent time pH < 4.0 and other variables key to disease severity to improve model precision and the diet treatment groups as indicator variables. We will determine *if the primary outcome (% time pH < 4.0)* differs by intervention arm. *We will use a linear mixed effects regression model to determine if percent time < pH 4 (Y_{ij}) differs by diet group. The model will incorporate the proportion of time each subject is observed so that subjects that drop out 2 or fewer weeks early are included in the analysis and allowed to have a smaller response to the diet intervention. In particular, for subject i at time j, $Y_{ij} = \beta + b_i + \beta_1 X_{1i} * t_{ij}) + \beta_2 X_{2i} * t_{ij}) + \beta_3 X_{3i} * t_{ij}) + \beta_4 X_{4i} * t_{ij}) + e_{ij}$ where $b_i \sim N(0, \sigma^2_b)$ is a subject specific random intercept used to account for repeated observations on the same subject, β is the mean at baseline, X_{pi} are indicator variables for diet group assignment with corresponding effects at 9 weeks β_p (p=1,..,4), and independent errors $e_{ij} \sim N(0, \sigma^2_e)$. The time the outcome is measured, t_{ij}, is included in the model such that $t_{i1} = 0$ at baseline, $t_{i2} = 1$ for subjects who complete the entire study, and $t_{i2} = p$ for subjects who leave after completing a proportion p of the weeks and come back for final pH testing. Subjects will be included if p >= 0.8.*

It is understood that some subjects may drop-out, and thus, not return for the final follow-up visit at week 9, in which case we would have missing values for some response variables. Frequently such dropouts are not a random sample of the entire cohort, and

analysis of only the complete cases would bias the results. *We will now request to subjects that inform of us they are dropping out between weeks 7 to 9 that they come in for a final visit. We have found that about 2/3 of subjects will agree to come in for a final visit even if they are not continuing to the end of study (week 9). This will significantly reduce the potential for missing data.* We will also attempt to obtain the specific reason for dropout on a case by case basis. Indirect information about the nonrandom dropouts will be obtained by using binary logistic models to predict the probability of dropping out using baseline variables. Thus, the impact of dropout on our results will be compared using assumptions that vary from missing completely at random to informative missing.

Sensitivity Analyses: We will use the daily diet data and daily medication checklist (type and amount) to conduct secondary analyses and verify the assumptions of our primary model. Summary statistics by diet group will be calculated to determine if weight loss, PPI use, total CHO, and simple CHO are consistent with the study design. We will also use the linear mixed effects model to determine if total and simple CHO are associated with total percent time < pH 4 by replacing the indicator variables in the primary model with these continuous covariates and their interaction. A secondary analysis of changes in PPI use over time will be considered. For this analysis, we will use the diary card data to create continuous variables of the weekly dose of PPI. PPI dose will be the outcome in a linear mixed effects regression model that includes time modeled flexibly using restricted and diet group indicators. An analogous model using weight as the outcome will be estimated. Our study is designed for subjects to maintain weight, but if weight loss differs by treatment arm, it may introduce confounding into our study. We will include weight loss as a covariate in our regression model to determine if our results are altered compared to the main analysis. This additional sensitivity analyses will be conducted as needed, for example where weight change is significantly different among groups, to assure effects are due to dietary not body weight change.

Interpretation: Given our expertise in nutrition, metabolism and obesity (Niswender and Silver), GERD (Smalley and Vaezi), and GERD biostatistics (Slaughter), our group is ideally suited for executing and interpreting this study. We predict that we will uncover key diet related factors driving GERD symptoms and esophageal acid exposure in the obese Veteran, and we will develop a predictive risk model based on sound science. Physiologically, the proposed study will determine whether changes in several plausible gut hormones and/or improvement in insulin sensitivity is associated with the improvement in GERD with the dietary intervention.

Our preliminary data suggest that reduction of simple carbohydrate was most robustly associated with GERD resolution. The current study design will more rigorously address whether it is simple or total carbohydrate that is the driver of GERD symptoms and reflux. This has important implications for the development of more broadly disseminated dietary recommendations; a moderately high carbohydrate but low simple carbohydrate diet may be more tolerable to certain individuals than a low total carbohydrate approach. Conversely, if total carbohydrate is determined to be the major factor in the response, we will by definition be suggesting fairly high-fat and high-protein dietary intakes. Such approaches are increasingly recognized to have efficacy for weight loss as well as improvement in cardiometabolic parameters such as lipid profiles. Although dietary fat intake has been positively associated with GERD in obese subjects,[52] the 4-5 investigations comparing effects of high fat to low fat diets on esophageal acid exposure and GERD symptoms have shown no worse outcomes with high fat diets.[20-23] Certainly in metabolically at risk populations (such as obese Veterans) we would be conscientious

regarding the source and composition of dietary fat intake, as well as the protein load of the diet.

The next level of analysis, for example, if lowering simple CHO intake reduces symptoms or esophageal acid exposure, will determine whether it is related to total dietary fiber intake or glycemic load. This analysis will reveal the extent to which "processing" of food ingredients contributes to GERD symptoms. The finding that higher dietary fiber and/or lower glycemic load is associated with less GERD would suggest that somewhat less of a focus on macronutrient composition (i.e., CHO *vs* fat) may be warranted, with more of a focus on consuming foods closer to their natural state.

Finally, by profiling several relevant gut hormones and assessing insulin sensitivity, we will investigate relationships for factors involved in plausible biological hypotheses for the effects of dietary carbohydrate on GERD symptoms. Our observation that reduction in simple CHO intake improves insulin sensitivity is consistent with a nutrient excess mechanism for insulin resistance. The mechanistic link between insulin sensitivity and GERD is most often considered in the context of weight loss, reduced waist circumference and improvement in abdominal pressures, and GERD symptoms. Here we investigate relationships that may suggest that improving insulin sensitivity independent of weight loss improves GERD. This has important implications for clinical translation, as induction of significant weight loss, and especially, long term maintenance of weight loss is a major clinical challenge. To reap clinical benefits on GERD and GERD symptoms without the requirement for weight loss would be a major clinical advantage. While gastrin release is not clearly understood to be differentially regulated by different macronutrients, GLP-1 and other gut hormones may well be. Thus, we will determine whether changes in the levels of any of the proposed gut hormones correlate with improvement in GERD. Identification of such an effect will drive specific hypotheses for future studies to uncover the mechanisms and clarify a mechanistic role in GERD response.

Thus, analysis of the data from the proposed study will determine which factor(s), fiber or glycemic load, total or simple carbohydrate, lower or higher fat in the context of more or less simple sugar, or gut hormones, should be targeted in next phase larger scale intervention studies. These findings will also drive the development of future experiments designed to understand the mechanistic effects of the optimal diet for GERD.

11.0 Privacy/Confidentiality Issues

All efforts, within reason, will be made to keep personal information in the participant's research record confidential. Careful safeguards are in place, and confidentiality will be maintained by coding data and blood samples using only a number to identify the data. The number assigned will be specific to this study and will not be related to other personal identifiers such as medical record number, telephone number, social security number or initials. The identification number will only be known to the study staff. The record linking the study number with the participant's name will be maintained by Dr. Niswender, Dr. Silver and the study team. It will be kept in a locked research office and in a locked file cabinet. Computer data will be password-protected.

The Sponsor and/or Vanderbilt may share the participant's information, without identifiers, to others or use it for other research projects not listed in this form. The Sponsor, Vanderbilt, Dr. Niswender, Dr. Silver and the study team will comply with any

and all laws regarding the privacy of such information. There are no plans to pay the participant for the use or transfer of this de-identified information.

In compliance with the National Institute of Health data sharing initiative, imaging data without any personal information attached may be shared with other investigators or public data repositories, which provides the research community with open access to datasets contributed by labs around the world. Information will be completely anonymized with demographics limited to age (accurate to the year up to 90 years old, or "90+" for older individuals), gender (male, female), group membership (e.g., disease/treatment state) and handedness. Data will be transferred using secure file transfer protocols.

12.0 Follow-up and Record Retention

Follow-Up: Since the study requires that obese subjects maintain their body weight during study, they will be provided with a meal plan for caloric restriction and nutrition counseling by the study dietitian upon completion.

Record Retention: The study results will be kept in the participant's research record for at least six years after the study is finished. At that time, the research data that has not been put in the medical records will be kept for an unknown length of time. Any research data that has been put into the medical records will be kept for an unknown length of time. Unless told otherwise, the participant's consent to use or share the PHI does not expire. If the participant changes his/her mind, he/she will be asked to contact Dr. Niswender in writing and let him know that he/she withdraws consent. Dr. Niswender's mailing address is: 315 Medical Arts Building, 1211 21st Ave South, Nashville, TN 37212. At that time, we will stop getting any more data about the participant, but, the health data we stored before the participant withdrew consent may still be used for reporting and research quality. If the participant decides not to take part in this research study, it will not affect treatment, payment or enrollment in any health plans or affect the ability to get benefits.

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