Protocol Title:	Socioecological Factors Associated with Ethnic Disparities in Bariatric Surgery Utilization and Post-Operative Weight Loss (Substudy)
Principal Investigator:	Benjamin Schneider, M.D.,
Population:	A subgroup of 100 adults 18-60 years old, with a BMI >35 kg/m^2 or who have had a weight loss surgery 8 months prior to enrollment will be invited to participate in this substudy.
Number of Sites:	UT Southwestern
Study Duration:	2 years
Subject Duration:	Approximately 1-2 weeks (cross-sectional)

General Information

- The prevalence of severe obesity has increased steadily in the United States population with ethnic minority groups being disproportionately affected. This study will allow the investigators to examine potential relationships between the blood and gut microbiotas of patients with obesity before and after weight loss surgery (WLS) and evaluate potential ethnic differences in the blood and gut microbiotas before and after the WLS.

Background Information

- WLS has become not only an increasingly utilized obesity treatment option when conventional lifestyle change methods (decreased caloric intake, increased activity levels) fail, but also a safe and medically effective treatment choice for severe obesity (body mass index [BMI] > 40 kg/m2 or > 35 kg/m2 with > 1 comorbidity),[1-6] type 2 diabetes[7-15] and other cardiometabolic risk factors.[16-27] In fact, a large body of evidence including 11 randomized clinical trials[28] indicate that WLS is a highly effective procedure that can also reduce blood sugar levels below diabetic thresholds. Based on this strong evidence, a Joint Statement endorsed by 45 professional organizations, diabetes clinicians and researchers recommend that WLS be a standardized treatment option for people with diabetes, including those who are mildly obese and fail to respond to conventional treatment.[28] Moreover, obese individuals who undergo WLS live higher quality and longer lives than those who do not undergo the procedure.[29-31]
- In the UT Southwestern WLS program, where approximately 400 surgeries are completed per year (> 6,000 since 2001; 60% Hispanic, 25% NHB, 5-10% multiracial, 5% NHW, 80% women), only 45-50% of the medically-referred patients who attend an initial education seminar complete WLS within a 12-15 month period. (NHB - Non-Hispanic Black; NHW - Non-Hispanic White)

  Findings from our research group show a lower post-operative weight loss in non-Hispanic Blacks than non-Hispanic Whites and Hispanics.[37] Reasons for the ethnic group disparities in post-WLS weight loss and comorbidity resolution are largely unknown.[39-41] Gut microbial composition could mediate, at least in part the discrepancies in the weight loss observed after WLS.[42-48] Specifically, NHB individuals experience significantly less post-surgery weight loss and diabetes-related improvement versus NHW.

In addition to gut microbial ethnic discrepancies, blood microbial differences could also be playing a factor in modulating the degree of weight loss or metabolic improvement post-surgery, however, no studies to this day have analyzed potential ethnic differences in blood microbial composition. Historically, blood has been considered as sterile and microbes were presumed to be only present in infections; however, bacteria have been shown to exist in the blood of healthy humans.[50-53] One hypothesis that explains the presence of blood bacteria is the translocation of gut bacteria into the circulatory system.[54,55] Gut dysbiosis, previous infections, and other inflammatory conditions increase gut permeability to bacteria by creating dysfunction in the intestinal epithelial barrier.[56,57,58] These mechanisms may explain the presence of blood bacteria in healthy individuals. Blood bacterial composition differs in people with infectious,[59,60] gastrointestinal;[61,62,63] cardiorespiratory;[64,65,66] and chronic inflammatory diseases.[67,68,69] Moreover, obesity can increase intestinal permeability, which may lead to elevated levels of bacterial translocation from the intestinal tract into the circulatory system. WLS has been shown to decrease intestine permeability.[70,71] Yet there have been no studies analyzing the blood microbiome in patients with obesity and/or in response to WLS.

Both blood and gut microbiotas have been related to the degree of fat mass loss and metabolic improvement after WLS.[72-78] Thus, it is possible that both microbiomes may afford a valuable source of novel biomarkers and targets for therapeutic modulation for this patient population. Considering that the gut microbiota could be the origin of the bacterial species present in the blood, it is important to investigate the relationship between the blood and gut microbial composition and how it is affected by WLS and ethnicity. Considering the above, we propose the following aims:

Substudy Objectives:

- **AIM 1.** Compare the relationship between the blood and the gut microbiomes among a sample of (1) pre-WLS and (2) 6-month post-WLS participants.
- *Hypothesis$_1$:* Blood bacterial composition will resemble that of the gut microbiome among pre-WLS participants. Because the effect of WLS on the blood microbiome is not known, our post-WLS results will be mostly exploratory.
- **AIM 2.** Determine racial differences in the blood microbiome of the pre- and post-WLS groups.
- *Hypothesis$_2$:* Ethnic differences will be detected in both the pre- and post-WLS groups.

Substudy Design

- A subgroup of participants from the main study will be invited to participate in a cross-sectional substudy evaluating the relationship between blood and gut microbiotas. A total of 100 participants will be recruited, with an aim for 50 participants to be recruited from the “non-completers” and the other 50 participants to be recruited from the “6 months post-WLS” follow-up group of our main project.
- From each of these subgroups, the target is for 50% to be NHB and 50% to be NHW. This is, by the end of the study we will have 4 groups: (1) no-WLS NHB, (2) no-WLS NHW, (3) post-WLS NHB, and (4) post-WLS NHW.

Substudy Population

- Inclusion criteria for substudy: Both groups will be 18-60 years old and will belong to either NHW or NHB ethnic groups. "No-WLS" participants will have a BMI >35 kg/m^2 (threshold BMI for WLS) whereas "6-8 months post-WLS" participants will have no BMI requirements.
- Exclusion criteria for substudy: having taken antibiotics in the previous 3 months; metformin, proton pump inhibitors, probiotics, or prebiotics in the previous month; currently following a vegetarian diet; pregnancy; having any infection in the previous month; having a comorbid disease that might alter the blood microbiome composition (e.g., renal failure) or the intestinal permeability (e.g., IBS); and having any electronic implants (e.g., pacemaker) or active prostheses.

- Recruitment Strategy for Substudy. By the time this IRB gets approved, all baseline samples from the main study would have already been collected. Therefore, we will recruit our non-surgery participants from the "non-completers" group from the main study. An email will be sent to all the participants that fall in this category and research spots will be provided on a first come first serve basis. Participants can e-consent online into the study. To recruit participants who have had bariatric surgery 6-8 months prior to their enrollment into the substudy, we will contact "early and late completers" who have already had the WLS but who have not done so more than 8 months ago. If additional participants are needed, particularly due to strict ethnic requirements (limited to NHW and NHB) we will first send invitation emails to the Weight Wellness Clinic patients, and if recruiting at the expected rate continues to be an issue we will advertise through IRB-approved flyers on social media or in the clinic setting.

Substudy Procedures

- Nutrition. Before each stool sampling point, participants will be asked to record their dietary intake for the previous 3 days. This will allow us to determine whether participants' diets affect the outcome of interest.

- Body Weight. Participants will be weighed using a SECA body composition scale. Participants will come to the clinic/laboratory in fasting conditions (8-12h fast). Height and waist circumference (at both the maximum abdominal protuberance and the umbilicus) will also be collected.

- Blood Samples. Two tubes of blood samples (20 ml) will be collected per participant after a fasting period of 8-12 hours. The venipuncture site will be first cleaned with alcohol and the first aliquot of blood drawn will be used for regular blood analysis (to exclude any potential skin contamination of the specimen that might affect blood microbial analysis) whereas the second tube will be used for gut microbial analysis. The EDTA tube will measure glucose, insulin, lipopolysaccharides, and lipopolysaccharides binding protein. The second tube (a Zymo DNA/RNA Shield blood collection tube [Zymo Research, R1150]) will be used for blood microbial analysis. To prevent host contamination from obscuring microbial signatures, before 16S rRNA sequencing is done, blood DNA will be eliminated using a protocol that depletes host cells.

- Stool Samples. Participants will self-collect stool samples and will store them in Zymo DNA/RNA Shield fecal collection tubes (Zymo Research, R1101) in their homes. Participants will bring the samples to their blood sample collection visit. Stool DNA extraction and 16S rRNA sequencing will be performed on these samples.

- 16S rRNA Analysis. The hypervariable region V3 and V4 of the bacterial 16S rRNA gene will be captured using the Illumina Nextera protocol (Part # 15044223 Rev. B; Illumina, San Diego, CA). A single amplicon of 460bp will be amplified using the 16S Forward 5'TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG and 16S Reverse Primer = 5'GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC, as described in the Illumina protocol. A subset of samples n= 50) will be analyzed using a whole-genome metagenomic sequencing approach to validate 16S data as well as to predict and explore the genes and potential functional aspects of detected microbiota. The polymerase chain reaction (PCR) product will be cleaned using Agencourt AMPure XP beads (Agencourt Bioscience Corporation, A Beckman Coulter Company, Beverly, MA). The Illumina adapter and barcode sequences will be ligated to the PCR amplicons in order to attach them to a MiSeqDx flow cell for multiplexing. The quality and quantity of each sequencing library will be assessed using a bioanalyzer and PicoGreen (Molecular Probes, Inc., Eugene, OR) measurements, respectively. About 6pM of pooled library will be loaded onto a MiSeqDX flow cell and sequenced using a PE300 (Paired end 300 bp) v3 kit. Raw FASTQ files will be demultiplexed based on unique barcodes and assessed for quality. Samples with more than 50K QC pass sequencing reads will be used for downstream 16S OTU analysis. Taxonomic classification and Operational Taxonomic Unit (OTU) abundance analysis will be done using a CLC Bio Microbial Genomics Module (QIAGEN, Redwood City, CA). Individual sample reads will be annotated with the Greengenes database, and taxonomic features of the sample will be determined. Blood microbiome compositions will be compared pre- and post-intervention. Alpha and beta diversity analyses will be computed to understand the within-sample and between-samples diversity, respectively. Raw FASTQ files will be submitted to the Sequence Read Archive (SRA).

Compensation Substudy

At the end of the substudy participants will receive a $100 USD Amazon e-card in appreciation of their participation. The card will be mailed electronically to the previously provided e-mail address within a week of completion.

Data and Safety Monitoring

All participants in the study will be evaluated for AEs from the time consent is signed through study completion or withdrawal. There are no anticipated adverse events for this study.

Adverse Events

For this study, an AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in study subjects, that is related to study. The following adverse events are expected/anticipated and should not be recorded for the purpose of this study:

- Discomfort at the site of blood draw
- Bruising, swelling, or bleeding around the site
- Lightheadedness/fainting
- Mild infection at the site of blood draw

Conditions/diseases that are chronic but stable should not be recorded as adverse events. Any changes in a chronic condition of disease that are consistent with its natural progression are also not considered AEs and should not be recorded.

Serious Adverse Events

Serious Adverse Events are defined as any event that results in death, is life-threatening, requires inpatient hospitalization or the prolongation of an existing hospitalization.

All adverse events will be monitored and tracked by the study team and/or Principal Investigator. These events will be recorded and reported via UTSW's HRPP Reporting Guidelines. The prevalence of adverse events, as needed, will be reported to UTSW IRB and NIH through annual reports.

All results of this trial will be reported yearly UT Southwestern's IRB. Trial procedures and progress as well as the occurrence of adverse events will be examined at 6-month intervals. Any action that results in the temporary or permanent suspension of the trial will be undertaken with consultation with the study's NIH project officer and the IRB.

Substudy Statistics

To measure the overlap between blood and gut microbiomes we will use weighted Jaccard indices. To compare alpha diversities between groups, Wilcoxon rank test on previously individually calculated Shannon indices (phyloseq) will be utilized.[141] PERMANOVA will be utilized to detect differentially abundance ASVs that represent OTUs in the bacterial genus or species level through DESeq2, edgeR, or metagenomicSeq.[142-144] For all analyses that involve multiple testing we will use the Benjamin Hochberg false discovery rate.[145]

Ethics

IRB approval will be sought from UT Southwestern under the UT System Reciprocity Agreement.
For the sub-group, participants who have already been enrolled in our main study will be the first invited to participate. If additional participants are needed, they will be invited through the Weight Wellness Clinic at UT Southwestern and through IRB-approved flyers posted on social media.

Data handling and record-keeping

Quality control and assurance. Online data storage and management will be accomplished via a RedCap database. Regarding data/records confidentiality, we have an established set of procedures designed to ensure the protection of confidentiality. All records on study participants will be stored in locked file cabinets in the office of the research team, who will maintain strict control over these records. As in our other studies, we will use a record system in which all participant records are filed according to their assigned subject ID. Access to the database and data files is strictly controlled by the Principal Investigator. Passwords are used to restrict entry into the database. Project staff is specifically trained on issues of confidentiality. Facilitators will also be trained on issues of confidentiality.

Quality Assurance: Accuracy and Completeness of the Data During Data Collection, Entry, Transmission, and Analysis. The project TBA lead coordinator will be entrusted with scanning spot check 10% of the data after entry to ensure accuracy and check questionnaires for completeness as they are collected. Field team staff will follow-up with study participants concerning questions that are skipped.
Participants are allowed to decline to answer but data checking is in place to ensure that data is not missing due to unintended circumstances.

Data Integrity. To maintain data integrity, fields within the RedCap database will have data type validation, simple ranges, and/or constraints. Data type validation will check that the entered data fits into the field type (i.e. a date field will only accept data entered in a date format). Simple ranges ensure that the data entered fits within the minimum and maximum values. Constraints check for invalid characters or values. Additionally more advanced checks can be done, such as cross-reference and

structured validations. Additionally, ad-hoc reports can be generated to check for data accuracy during the data collection process. Access to this feature will be restricted to required users using user privileges.

Data Export for Analysis. Data can be exported out from RedCap in various ways and in various formats. Data may be exported as a CSV (comma-delimited) file from a report or as a PDF file from the data entry page when viewing a particular record. Additionally, all collected data can be exported to CSV, XML, DBF, or Microsoft Excel file types. This interface allows for direct data importing, running SQL queries, generating ad-hoc reports, and accessing the data in real time. Access to these features will be restricted to authorized users using user privileges.

Data Confidentiality, Storage and Preservation. The PI and study team will have access for any required data cleaning. At the completion of the proposed study, access to database will be removed for all nonessential team members and further data modification will be disabled. All data will then be transferred from the database server into a 256-bit AES encrypted archive file and will only be accessible to the PI and a secondary co-custodian.

All participants will be assigned a unique code number by RedCap or the study team. This ID number will be used on all response forms, spreadsheets and data files to ensure participant confidentiality. Participant name, address, telephone, and any other means of identification will be destroyed following the completion of study using methods outlined by the UTSW HRPP office. All study personnel are equipped with password protected personal computer access and password protected access to a network drive accessible only from project staff computers. All computers and network drives are maintained by UT Health's Information Technology Department (IT).

Data Security. For added security and reliability, RedCap is separated into two servers, a web server and a database server. Data entry is done through the web server only and users do not have direct access to the database server. Both servers will be managed by UT Health's Information Technology and are physically located at its data center and covered by its security policies. Which include continuous network scans, penetration testing, daily patches, off-site tape backups, and other enterprise-level data management procedures. Additional security is implemented at the application level. RedCap maintains a built-in audit trail that logs all events, user access, and data creation and modifications. Log files can be exported for analysis and reporting purposes. All collected data is backed up hourly with redundant nightly backups stored to a separate server going back 6 months. Database consistency checks for errors and server maintenance also occur daily.

Finally, PI and the research team will meet regularly and follow appropriate compliance guidelines regarding data and safety.

Publication Plan

Results from this study will be published in leading peer-reviewed journals. Additionally, preliminary findings and analyses will be submitted to leading national and international research meetings in the field. The PI anticipates a minimum of 2 manuscripts published from the substudy. These aggregate results will be available to research subjects and they will be made aware of their existence.

ATTACHMENTS

1. Schematic of Study Design
2. Study Schedule
3. Consent Document

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