Feasibility and Acceptability of a Beverage Intervention for Hispanic Adults

NCT02911753 (ClinicalTrials.gov)

Registered September 19, 2016. Last updated November 1, 2017

Aims and Study Hypotheses

This pilot study will expand on earlier research by our team using beverage interventions to enhance cardiometabolic health. This study's primary objective is to assess the feasibility and acceptability of a beverage intervention in obese Hispanic adults. Primary feasibility outcomes will be recruitment, retention, and acceptability. Beverage intake will also be assessed through intake diaries and beverage return rates during weekly clinic visits. The preliminary efficacy of the beverage intervention will assess changes in total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) over 6-weeks. Secondary outcomes are changes in fasting glucose, hemoglobin A1c (HbA1c), and high-sensitivity C-reactive protein (hs-CRP). Our study will evaluate participant-reported tolerance and as an exploratory aim, our study will also assess safety/toxicity-related to renal and/or liver function as albeit limited, evidence from green tea polyphenol E supplementation studies have reported a few cases of hepatic toxicity with on-going supplementation [1]. Renal and hepatic toxicity function will be assessed at baseline and 6-weeks. The aforementioned outcomes will be examined to test the following hypotheses: a) recruitment and retention of obese Hispanic participants in a 6-week beverage intervention study is feasible; b) the consumption of green tea and Mediterranean lemonade will be well-tolerated with high adherence; and c) green tea and Mediterranean lemonade intake will result in an improved cardiometabolic profile at the end of 6-weeks.

Design and Methodology

Design

This study is a pilot randomized controlled trial where participants are randomized to one of three beverages: Green Tea (GT), Mediterranean lemonade (ML), or a Flavored Water control (FW). Participants will be stratified by gender using block randomization and an allocation ratio of 2:2:1 with variable block sizes. A computer randomization system will be used to complete the randomization assignment. We propose to consent 150 individuals to randomize 50 participants into our 6-week study. Following consent and baseline assessments, randomization assignment will be determined and documented in the participants' study record and shared with the participant. Assessments will be performed by blinded study personnel. Under no circumstances will unblinding be permissible. Investigators, intervention staff, and participants will not be blinded for the study. The schedule of the enrollment, interventions, and assessments according to SPIRIT requirements is shown in **Figure 1**.

Figure 1. Content for the schedule of enrollment, interventions, and assessments according to SPIRIT requirements

	STUDY PERIOD			
	Enrollment	**Allocation**	**Post-allocation**	**Close-out**
TIMEPOINT**	$-t_1$	**0**	t_1	t_x
ENROLLMENT:				
Eligibility screen	X			
Informed consent	X			
2-Week Run-In	X			
Allocation		X		
INTERVENTIONS				
Green Tea			←	→
Mediterranean Lemonade			←	→
Flavored Water Control			←	→
ASSESSMENTS:				
Anthropometry			X	X
Cardiometabolic Measures			X	X
Self-Reported Questionnaires			X	X

Setting of the Human Research

Research activities will take place at the University of Arizona Collaboratory for Metabolic Disease Prevention and Treatment in Tucson, AZ. All procedures have been approved by the University of Arizona Institutional Review Board.

Study Population

We will recruit 50 obese Hispanic adults aged 18-64 years living in the Tucson area. Individuals will be considered eligible if they met all of the following criteria: self-identified as Hispanic, 18-64 years of age, BMI between 30-50.0 kg/m², able to provide informed consent, and able to speak, read, and write in either English and/or Spanish. Individuals were excluded if they met any of the following criteria: diagnosis of diabetes mellitus; history of liver disease; current medication for glucose control; cholesterol control; uncontrolled blood pressure; current eating disorders such as anorexia nervosa; bulimia, etc. (likely to make adherence to prescribed beverage intake difficult); current alcohol or substance abuse; currently treated for psychological issues (i.e. depression, bipolar disorder, etc.); taking psychotropic medications within the previous 12 months or hospitalized for depression within the previous 5 years; report exercise on ≥3 days per week for ≥ 20 minutes per day over the past 3 months; reported weight loss of ≥5% or participating in a weight reduction diet program in the past 3 months; reported plans to relocate to a location that limits their access to the study site or having employment, personal, or travel commitments that prohibit attendance to all of the scheduled assessments; reported plans to relocate to a location that limits their access to the study site or having employment, personal, or travel commitments that prohibit attendance to all of the scheduled assessments; or reported

consumption of ≥ 1 cup of green tea and/or citrus fruit daily and were not willing to complete 2-week run-in period.

Study Recruitment

Recruitment efforts will primarily target local community-based settings such as clinics, health fairs, and outdoor marketplaces frequented by Hispanic communities in Tucson, AZ. Additional recruitment strategies included the use of social media posts (e.g., Facebook, and Craigslist) and health provider initiated approaches (e.g., patient referral). Participants of preliminary studies who had expressed interest in health behavior research and had signed consent to be contacted for future intervention studies also were contacted. Potential participants were instructed to call study staff and a telephone screening was conducted to determine initial eligibility. Interested individuals engaged at recruitment settings were given the option of being screened on-site or during a future phone call with study staff. Telephone and on-site screenings included a detailed description of the study and its potential risks and benefits. Upon the participants' verbal agreement, study staff asked questions regarding medical history and other pertinent questions related to exclusion/inclusion criteria.

Informed Consent

All eligible participants will be invited to the Collaboratory where complete details of the study will be provided in the participants' preferred language (Spanish or English). During this time, participants will be encouraged to ask questions about the study's procedures. Interested

participants will provide written informed consent to study personnel using consent forms that are available in the participants' preferred language.

Certificate of Confidentiality

To help us protect the participant's privacy, we obtained a Certificate of Confidentiality (CC-DK-17-003) from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This Certificate can be used legally to refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena.

Study Intervention

Study personnel will prepare all study beverages. Lipton® Decaffeinated Green tea will be prepared using a ratio of 4 tea bags per 32 oz. water. Upon reaching a boil, tea bags will be steeped into water for 3-5 minutes. When slightly cooled, 4 drops of Liquid No Calorie Stevia™ will be added per 32 oz. of tea. To prepare the Mediterranean lemonade, two full lemons will be de-seeded and blended with 32 oz. of water and 4 drops of Liquid No Calorie Stevia™. The control beverage will be prepared using 4 drops of Crystal Light Liquid Drink Mix (strawberry lemonade) per 32 oz. of water. All beverages will be prepared two days prior to participant pick-ups. All green tea will be kept frozen while the Mediterranean lemonade and flavored water will be refrigerated for storage and distribution to study participants. Preparation and storage procedures were informed by prior chemical analysis of bioactive components in the beverages across seven days to assure optimal exposure. Mean epigallocatechin gallate (EGCG), the main

polyphenol found in green tea, was 161.5 mg per 32 oz. and mean *d*-limonene was 373.4 µg/ml per 32 oz. in the Mediterranean lemonade. All analyses were conducted by the UA Cancer Center Analytical Chemistry Shared Resource.

Participants will complete a 2-week run-in period prior to beginning the 6-week intervention. During this period, participants will be asked to stop all tea and citrus fruit consumption and limit consumption of any beverages except water. Each participant will be provided with a 32-ounce Hydro Flask® to support regular intake of the prescribed beverage. This run-in period will determine the feasibility of consuming 32 oz. each day for participant adherence to the beverage intervention.

Upon successful completion of baseline assessments and 2-week run-in, participants will be randomized to a beverage assignment. All participants will be advised to consume the entire beverage assigned on a daily basis (rather than save up and consume large amounts on fewer days). At the start of the intervention, participants will be asked to continue avoiding all other sources of tea, lemonade, and citrus, limit coffee consumption to 2 cups/day, avoid all sweetened beverages other than study-provided drinks, consume water ad lib, and avoid alcohol in excess of 1 drink/day for women and 2 drinks/day for men. In addition, participants will be asked to self-monitor their beverage consumption behaviors using a weekly journal to help habitually regulate beverage intake. Participants will be responsible for picking up one week's worth of beverages once per week from the study clinic. Participants will be asked to return any un-consumed beverages during weekly pick-ups; study staff will measure and record any amount not

consumed. Weekly beverage journals will also be collected and new ones distributed for use the following week. Brief in-person interviews or "check-ins" lasting 5-10 minutes will also take place during this time with bilingual study staff. These interviews will follow a script to review beverage-related behaviors and identify and address specific barriers for adherence to study beverage intake.

Retention Strategies

We will use common strategies to enhance participant retention, including: 1) collecting contact information of participants and at least two family members; 2) program reminders; 3) incentives to complete assessments; and 4) contacting participants at their preferred time by their preferred method (i.e. call or text) in their preferred language.

Participant-Reported Tolerance or Toxicities

Potential risks may include but are not limited to: nausea, vomiting, frequent bowel movements, flatulence (gas), acid reflux, excess burping, heartburn, and bloating. If a participant experiences any of these signs/symptoms associated with beverage intake, they will be given the option to withdraw from the study or change to the alternate beverage intervention (but not flavored water) after a 1-week washout period. Participants will be asked on a weekly basis about any issues related to their beverage consumption and this information will be noted. Prior literature has reported a few cases of hepatic toxicity related to supplementation with high-dose green tea polyphenols [1]. No evidence exists to suggest toxicity or safety issues related to the green tea nor Mediterranean lemonade beverages consumed in the amounts prescribed for this study.

Therefore, renal and hepatic function will be monitored at study beginning and end using alanine transaminase (ALT) or aspartate transaminase (AST) values. Abnormal values will be shared with the participant and the participant will be advised to visit their physician for evaluation. In the event this occurs, participants will not receive additional compensation and the study will not cover additional costs for physician follow-up.

Methods for Assessing Study Outcomes and Potential Confounders

Anthropometry

Height, body weight, waist circumference, and resting blood pressure will be measured at baseline and 6-weeks. Height will be measured to the nearest 0.01 centimeter (cm) using a ShorrBoard® wall-mounted stadiometer with participants removing their shoes prior to the measurement. Two measurements will be taken. A third measurement will be taken if the first two measurements differ by more than 0.5 cm. The average of the two measurements which met the criteria above will be recorded for data collection. Body weight will be measured using a Seca 876 scale to the nearest 0.1 kilogram (kg) on a digital scale without shoes. Two measurements will be taken. A third measurement will be taken if the first two measurements differ by more than 0.2 kg. The average of the two measurements which meets the criteria above will be recorded for data collection. BMI will be calculated using body weight in kilograms divided by squared height in meters (kg/m^2). Waist circumference will be obtained using a Gulick measuring tape recorded to the nearest 0.1 cm. Waist circumference will be measured in the horizontal plane directly at the umbilicus. Two measurements will be taken at each site. A third measurement will be taken if the first two measurements differ by more than 2.0 cm. The average of the two measurements closest to each other will be recorded for data collection.

Resting blood pressure and heart rate will be measured using the Omron Digital Blood Pressure Monitor HEM-907XL on the participant's left arm. Using a Gulick measuring tape, an arm measurement will be performed on the lateral aspect of the left arm at the midpoint between the acromion process to the olecranon process to determine the appropriate cuff size. Upon a five-minute resting period with the participant in an upright position with feet flat on the floor, two blood pressure measurements will be taken with a one-minute time period between each measurement. A third blood pressure will be taken if the mean difference between the systolic blood pressure measurements differs by 10 mmHg or greater and/or the diastolic blood pressure measurements differs by 6 mmHg or greater. The average of the two measurements which meets the criteria above will be recorded for data collection. In addition, if the mean resting systolic blood pressure is ≥150 mmHg or average diastolic blood pressure is ≥100 mmHg at baseline, the participant will be excluded from participation and referred back to their physician.

Biological Samples

Emerging evidence indicates that genetic variation may impact the efficacy of lifestyle behavioral interventions [2]. Therefore, we will perform a buccal cell collection by using a cytology brush to brush the inside of each check for 30 seconds for the extraction of DNA and subsequent genetic analyses. This optional non-invasive, self-collection of buccal cells will occur at one time and will be performed at either the baseline (preferable) or follow-up visit. Participants also will have the option of allowing the study investigators to store some of the blood that was taken but not used for other tests. This will allow the researchers to derive metabolomics and molecular data that are complementary in obesity research and provide value for enhancing precision care in this health disparate population.

Cardiometabolic Measures

Fasting blood samples (venipuncture; 25 mL), will be collected at baseline and 6-weeks, by a trained phlebotomist, for the purpose of examining the following cardiometabolic measures: total cholesterol, triglycerides, HDL, LDL, very low-density lipoprotein (VLDL), HbA1C, hs-CRP, and fasting glucose. A comprehensive metabolic liver/kidney panel will be performed to assess the following: albumin, globulin, A/G ratio, total protein, alkaline phosphatase, ALT, AST, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, BUN/creatinine ratio, glomerular filtration rate/estimated, and electrolytes (sodium, potassium, chloride, carbon dioxide). All laboratory tests will be performed by an independent, clinical lab (Banner University Medical Center, Tucson, AZ), blinded to the study outcomes.

Physical Activity

Physical activity will be assessed at baseline and 6-weeks using the Global PA Questionnaire (GPAQ) [3, 4]. It is available in both English and Spanish and provides minutes/week of physical activity of varying intensity and type. The GPAQ has been validated compared to accelerometer data in determining time spent in moderate-to-vigorous physical activity (MVPA) and to assess changes in physical activity over time. Cleland et al. [4] found a moderate agreement between the GPAQ and accelerometer for MVPA mins/day ($r = 0.48$) and results for agreement in changer over time showed moderate correlation ($r = 0.52$, $p = 0.12$). Similar correlations have been reported for the GPAQ compared to accelerometer data for Hispanic women participating in a 6-month physical activity intervention [3].

Diet

Diet assessment will be completed at baseline and 6-weeks using the Southwestern Food Frequency Questionnaire (SWFFQ) [5-7], a bilingual FFQ that includes food items commonly consumed by Mexican Americans and uses Mexican names for food items commonly given different names by other Spanish speakers (e.g., “naranja”, not “china”, for “orange”). Output data from the SWFFQ will allow us to calculate daily intake of total sugar, saturated fat, sodium, fiber, whole grains, and fruits/vegetables. Internal validity of the SWFFQ compares favorably with 24-hour recall (r=0.82) [5]. SWFFQ data will be analyzed using the 2009 United States Department of Agriculture (USDA) Nutrient Data Bank.

Tea Consumption

We will assess tea consumption at baseline and 6-weeks using the Arizona Tea Questionnaire. This 28-item scannable questionnaire has been tested for short and long-term reliability as well as relative validity [8]. This questionnaire asks about usual tea intake over the past year, as well as lifetime consumption patterns including amount, type, and preparation technique. The output is provided in total flavonoids, total polyphenols, catechins, theaflavins, thearubigins, caffeine, and gallic acid.

Psychosocial Measures and Acculturation

We will use the following self-reported questionnaires to assess psychosocial measures at baseline and 6-weeks which may influence diet and physical activity behaviors: Self-efficacy [9] and social support for diet [10], The Acculturation Rating Scale for Mexican Americans–II (ARSMA-II) [11] will be used to measure acculturation related to language, ethnic identity, and

ethnic interaction. The reliability, and validity of the ARSMA-II are well established in English and Spanish [11].

Statistical Analysis Plan

Feasibility outcomes

The primary feasibility outcomes are recruitment and retention. We aimed to recruit, on average, approximately 2-3 participants per week during the active recruitment phase. A recruitment rate of less than this would indicate a lack of feasibility. We recorded the number of Hispanic adults who contacted the researchers and expressed interest in participation, the number screened for eligibility, and the number ineligible for study inclusion and the reason for their ineligibility. Retention will be assessed by calculating the proportion of participants who completed the study out of the number enrolled, with a 95% confidence interval.

Treatment Satisfaction/Acceptability

At the completion of the study, participants will take part in an exit interview where they will be asked to rate their overall satisfaction with the intervention, if they would consider a longer-term beverage intervention, and finally, if they would recommend the program to others. Participants will also be asked questions regarding satisfaction with their overall progress and for changing dietary beverage habits. Each item will be rated on a Likert scale with higher scores indicating greater program favorability. Open-ended questions will be used to seek participant input on modifications that could be made to improve acceptability and effectiveness of the intervention.

The responses will be used to identify which recruitment and intervention components were well received, which could be improved, and which were not acceptable.

Efficacy Outcomes

Descriptive statistics, including means, ranges, and standard deviations, will be calculated for the primary efficacy outcomes, cholesterol/lipid levels, and the secondary outcomes: fasting glucose, HbA1c, and hs-CRP. Mixed models will be used to compare arms in each of these outcomes' change from baseline. We will include fixed effects of intervention arm, time and their interaction to allow for different patterns of change between the arms, as well as a random participant effect to account for the longitudinal nature of the data. Baseline values of the outcomes will be included in the dependent variable vector. The changes from baseline, and the differences between arms in change from baseline will be estimated using contrasts from the mixed models. Mixed models yield unbiased estimates for data that are missing completely at random (when missingness does not depend on any observed or unobserved data) and missing at random (when missingness may depend on observed data, such as the baseline value of the outcomes), as these models perform an implicit imputation [12, 13]. Data from all patients who are randomized will be analyzed in the arm that they were randomized to.

Sample Size Calculation

The total sample size of 50 will provide 95% confidence intervals for the primary feasibility outcomes (proportion of eligible participants who enroll and the proportion of participants retained in the study) that are no wider than 0.28 (±margin of error = 0.14), conservatively assuming a base proportion of 0.5, which maximizes the standard error. The trial will be

considered feasible if the proportion retained is greater than 70%. If retention in the study is 81% or greater, the 95% confidence interval will not contain this 70% cutoff. Power will be insufficient to detect a minimum important difference of a 6 mg/dL change in fasting lipids from baseline, the primary efficacy outcome, based on variance estimates from a trial using a different fruit [14] (standard deviation ≈25mg/dL). We acknowledge that we are not sufficiently powered to detect important differences between arms, but if the 95% confidence intervals for the comparison of the arms contain important differences we will take this as indication of a promising intervention. Variance components estimated from this study will be used to design an adequately powered trial.

Data Management

Data management will be conducted according to Good Clinical Practice guidelines to enhance data quality assurance and control. This will include standard operating procedures and staff trainings for data acquisition, entry, and processing. Further, information obtained from this research will be kept confidential to respect the participant's privacy. All records will be stored and locked in a file cabinet. In addition, all research databases will have password-controlled access, and the researchers will control this access. Data analyses will take place using a dedicated study computer upon study completion. No interim analyses will be performed. Study data will be uniquely coded for each subject and then entered via secure server to a Research Electronic Data Capture (REDCap) database maintained by the Clinical and Translational Sciences Research Center (CATS) at the University of Arizona. Only local study personnel will have access to identified study data. Once the study is complete the study records will be transferred to the University of Arizona storage facility and kept in accordance with applicable

laws. All participant data (including signed informed consent) will be stored for 6 years after the completion of the project. Results from this study will be disseminated through peer-reviewed manuscripts and presentations at national meetings. Participants will be provided with a lay summary of the research findings and the peer reviewed manuscripts.

List of Abbreviations:

Center of Disease Control (CDC)

Body mass index (BMI)

Epigallocatechin gallate (EGCG),

Sugar-sweetened beverages (SSBs)

hs-CRP (high-sensitivity C-reactive protein)

HDL (high-density lipoprotein)

LDL (low-density lipoprotein)

VLDL (very low-density lipoprotein)

HbA1c (Hemoglobin A1c)

Alantine transaminase (ALT)

Aspartate transaminase (AST)

Blood urea nitrogen (BUN)

United States Department of Agriculture (USDA)

References

1. Isomura T, Suzuki S, Origasa H, Hosono A, Suzuki M, Sawada T, Terao S, Muto Y, Koga T: Liver-related safety assessment of green tea extracts in humans: a systematic review of randomized controlled trials. *Eur J Clin Nutr* 2016, 70:1340.
2. Bray MS, Loos RJF, McCaffery JM, Ling C, Franks PW, Weinstock GM, Snyder MP, Vassy JL, Agurs-Collins T, The Conference Working G: NIH working group report—using genomic information to guide weight management: From universal to precision treatment. *Obesity* 2016, 24:14-22.
3. Hoos T, Espinoza N, Marshall S, Arredondo EM: Validity of the Global Physical Activity Questionnaire (GPAQ) in adult Latinas. *Journal of physical activity & health* 2012, 9:698-705.
4. Cleland CL, Hunter RF, Kee F, Cupples ME, Sallis JF, Tully MA: Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour. *BMC public health* 2014, 14:1255.
5. Taren DL, Tobar M, Ritenbaugh C, Graver E, Whitacre R, Aickin M: Evaluation of the Southwest Food Frequency Questionnaire. *Ecology of Food and Nutrition* 2000, 38:515-547.
6. Martinez ME, Marshall JR, Graver E, Whitacre RC, Woolf K, Ritenbaugh C, Alberts DS: Reliability and validity of a self-administered food frequency questionnaire in a chemoprevention trial of adenoma recurrence. *Cancer Epidemiol Biomarkers Prev* 1999, 8:941-946.
7. Garcia R, Taren DL, Teufel N: Factors associated with the reproducibility of specific food items from the Southwestern Food Frequency Questionnaire. *Ecology of Food and Nutrition* 1999, 38:549-561.
8. Hakim IA, Hartz V, Harris RB, Balentine D, Weisgerber UM, Graver E, Whitacre R, Alberts D: Reproducibility and relative validity of a questionnaire to assess intake of black tea polyphenols in epidemiological studies. *Cancer Epidemiol Biomarkers Prev* 2001, 10:667-678.
9. Sallis JF, Pinski RB, Grossman RM, Patterson TL, Nader PR: The development of self-efficacy scales for healthrelated diet and exercise behaviors. *Health Education Research* 1988, 3:283-292.
10. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR: The development of scales to measure social support for diet and exercise behaviors. *Preventive Medicine* 1987, 16:825-836.
11. Cuellar I, Arnold B, Maldonado R: Acculturation rating scale for Mexican Americans-II: A revision of the original ARSMA Scale. *Hispanic Journal of Behavioral Sciences* 1995, 17:275-304.
12. Bell ML, Fairclough DL: Practical and statistical issues in missing data for longitudinal patient-reported outcomes. *Stat Methods Med Res* 2014, 23:440-459.
13. Molenberghs G, Thijs H, Jansen I, Beunckens C, Kenward MG, Mallinckrodt C, Carroll RJ: Analyzing incomplete longitudinal clinical trial data. *Biostatistics* 2004, 5:445-464.
14. Dow CA, Going SB, Chow HH, Patil BS, Thomson CA: The effects of daily consumption of grapefruit on body weight, lipids, and blood pressure in healthy, overweight adults. *Metabolism* 2012, 61:1026-1035.