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Legume Diet Satiety and Weight Loss Pilot Study

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1. INTRODUCTION

Obesity is a significant public health concern. Nearly two-third of US adults are overweight or obese (body mass index [BMI] $\geq$25 and $\geq$30 kg/m^2, respectively).[1] It is well known that excess body weight is associated with increased risk for a number of chronic conditions including diabetes, heart disease, and some cancers including colorectal cancer (CRC).

Effective dietary strategies are essential to address the issues of obesity and related metabolic disorders. Diet composition is one factor that could influence dietary energy intake. For example, diets that are high in fiber require more chewing and a greater volume is consumed at a given energy intake (kcal/g). These factors could lead to earlier termination of eating and increased satiation. In addition, fiber-rich diets may impact physiological mechanisms important for weight control including hormone release and gastric emptying.[2,3]

Epidemiologic research has linked higher legume consumption with reduced risk for obesity[2] and in some studies, with reduced risk for CRC and the precursor lesions, adenomatous polyps.[4] In previous research that targeted men at increased risk for CRC we observed that a high-legume diet provided under conditions of weight maintenance favorably influenced biomarkers of inflammation, lipid levels, and gut hormone concentrations.[5-9] In the same study, during a 4-week ancillary diet period where participants consumed the full legume diet entrée but with side dishes ad libitum and were allowed to lose weight, the high-legume diet facilitated weight loss.[8] Participants consumed less total energy (-770 kcal/d below requirements for weight maintenance), lost weight (-4.0 kg; -4.4%) and serum lipid and gut hormone concentrations and biomarkers of insulin sensitivity (plasma glucose: -5.7%; insulin: -15.8%; serum C-peptide: -17.4%) and inflammation (serum CRP: -20.2) all improved significantly. This sub-study was conducted after an intensive 12 week randomized controlled crossover feeding trial but the sub-study itself was not randomized and controlled. We did not have the resources needed to conduct a feeding response time-course experiment or to explore other novel mechanisms through which legumes may facilitate weight loss (e.g. appetite-regulating hormones, gastric emptying and transit time). In addition, the provision of all of the diet components may have played a role in controlling intake and promoting weight loss.

The goal of the currently proposed study is to build upon our previous findings by conducting a randomized controlled feeding pilot study within a more diverse population also at high risk for CRC to evaluate whether a high-legume diet will result in increased satiety and in turn will facilitate reduced energy intake and weight loss compared to a control diet provided under similar conditions. In addition, we will explore potential beneficial effects of the high-legume diet on gastric emptying and circulating levels of appetite-regulating hormones and other biomarkers. Dietary behaviors that are even moderately more satiating over time have the potential to enhance weight loss and could lead to a significant public health impact among populations at high risk for CRC and other chronic diseases.

1.1. Study Objectives

This pilot randomized trial will evaluate the effects of diet composition, comparing a legume-rich diet and a control diet, on weight loss over the course of eight weeks. The primary outcome is weight loss. Secondary objectives will compare the effects of the two diets on total energy intake, biomarkers related to appetite regulation and blood glucose control and in exploratory

analyses will assess other aspects related to weight loss (e.g., effects on gastrointestinal emptying and transit time and on gut microbiota).

1.1.1. Primary Objectives

1. Evaluate the effects of a high-legume diet compared to a control diet with a similar macronutrient profile on weight loss in a randomized controlled feeding study conducted over eight weeks.

1.1.2. Secondary Objectives

1. Assess whether the legume diet reduces the average daily dietary energy intake of participants compared to a controlled diet.
2. Compare satiety of the high-legume diet to the control diet using self-reported satiety questionnaires.
3. Assess the effects of the two diet treatments on fasting levels of C-reactive protein (CRP, a marker of inflammation) and total cholesterol level.
4. Evaluate the effects of the aforementioned diet treatments on markers of appetite regulation (cholecystokinin – CCK) and insulin resistance (insulin, glucose) in a meal response time course experiment.
5. Compare the effects of the high-legume and control diets on gastric emptying time and gut transit time.
6. Evaluate diet-related changes in fecal biomarkers associated with CRC risk.

1.2. Background and Rationale

1.2.1. Scope of the problem

Colorectal carcinoma (CRC) is the second leading cause of cancer death in the U.S.[10] Adiposity is a well-known risk factor for CRC and for colorectal adenomatous polyps[11], recognized as precursor lesions for the majority of CRCs[12]. A significant body of literature suggests that weight and body fatness are positively associated with increased risk for adenoma incidence. More recently investigators have shown that obesity and body fatness are linked with recurrence for colorectal adenomas, particularly among men.[13] The influence of weight change, particularly weight loss, on risk factors for CRC and adenomatous polyps has been examined in only relatively few studies.[14,15] A three-year multicenter trial to prospectively address this question is in progress.[16,17]

1.2.2. Insulin resistance (IR) and colon cancer mechanisms

Insulin resistance, the impairment to the biological response of insulin action, is characterized by compensatory hyperinsulinemia and increased risk for Type-II diabetes (DM).[18] Obesity is a well-known risk factor for insulin resistance and DM. A number of epidemiologic studies have provided convincing evidence for an association between DM and CRC.[19-21] Exposure to elevated insulin, glucose, and triglycerides could affect growth, development, and homeostasis of colonic cells.[22,23] Recently, Komminou and colleagues reviewed the mechanistic associations between insulin resistance and CRC, as seen in **Figure 1.**[24] Inflammation and cytokine production such as TNF-α, are thought to promote insulin resistance,[23] increase IFG-1, and activate IκB kinase β (IKKβ), an upstream activator of NF-κB which leads to increased proliferation and decreased differentiation and apoptosis.[24]

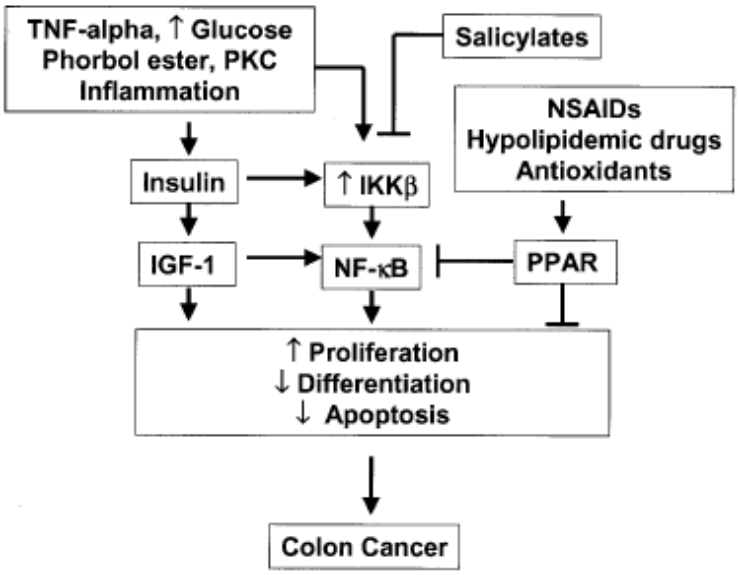


Figure 1. Mechanistic association between insulin resistance and colon cancer

1.2.3. Inflammation, insulin resistance and CRC

C-reactive protein (CRP), an acute phase protein, is thought to be a sensitive and particularly stable marker for sub-clinical inflammation. Cytokines, mainly interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) may exert major stimulatory effects on the hepatic synthesis of acute-phase proteins.[25] Elevated levels of CRP are commonly found among overweight and obese individuals and are known to predict the development of insulin resistance[26-30] and type-II diabetes.[31-33]. Inflammation creates a microenvironment that encourages neoplastic transformations and potentiates the progression of cancer. In a recent cohort study[34] plasma CRP concentrations were higher among CRC cases than controls (median CRP, 2.44 vs. 1.94 mg/L; P =.01) and risk of CRC was higher in persons in the highest quartile of CRP (OR= 2.55; 95% CI, 1.34-4.88; P for trend =.002). In our previous feeding study we demonstrated that CRP levels decreased by over 20% in response to a mean weight loss of 4.0 kg in men at high risk for CRC.[8]

1.2.4. Legumes

Despite the fact that at least 58 studies have evaluated the association between legumes and cancer risk,[35,36] there is no clear pattern of increased or decreased risk. One potential problem in investigating the relationship between legume intake and CRC is the low intake of legumes in economically developed countries that have a higher CRC incidence.

Intake of legumes provides benefits in reducing risk for diabetes and in diabetes management. Pulses (dry beans) are high in fiber and have a very low glycemic index (GI)[37] indicating that after eating pulses, the blood glucose increase is much less than with most polysaccharide-rich foods. Several studies suggest that the intake of pulses offers important benefits for the management of diabetes.[38-41] Legumes have also been shown to increase satiety compared to legume-free meals with the same energy content, and randomized trials of legume consumption on weight loss have been generally positive, though energy restriction appears necessary.[2]

1.2.5. Polyp Prevention Trial (PPT) Data

The strongest dietary association in the PPT cohort was an inverse association between legume intake and advanced adenomas. Those in the highest quartile of average dry bean intake had a

significant reduction in their odds ratio for recurrence of advanced polyps (OR=0.30 95% CI; 0.15-0.60). For males, increased legume intake was also associated with a reduced odds ratio for any adenoma recurrence (OR=0.69 95% CI; 0.48-0.99)[4]. The intervention arm, who consumed more legumes overall, also lost significantly more weight than the control arm,[42] supporting the hypothesis that a high fiber diet may help with weight management.

1.2.6. Satiety

A high fiber diet increases the volume of food compared to the number of calories consumed (i.e., decreases energy density – ED kcal/g), which creates a greater feeling of gastric fullness for fewer calories.[43] Increased fiber content prolongs the postprandial presence of intestinally derived lipoproteins and augments the release of cholecystokinin (CCK), a major gut peptide and a potent satiety signal involved in meal termination.[44]. Several controlled feeding studies with high legume diets have shown increases in CCK.[45,46] The working hypothesis is that continued consumption of a high-legume, high-fiber diet will result in changes in circulating levels of CCK and related biomarkers measured post-prandially.

1.2.7. Gut Microbiome

A high fiber diet has been known to alter the gut microbiome of individuals provided the duration of the intervention is long enough. Certain intestinal microbiota have been associated with increased or decreased levels of inflammation and obesity. Fiber intervention trials in both human and animal models have shown a decrease in inflammatory response with increasing fiber.[47] It is unclear whether this effect is at least partially the result of changing gut microbiome composition or if it is a side effect of the fiber-inflammation relationship.

1.2.8. Gastric emptying and GI transit time

The addition of a high-fiber ingredient to a low fat meal can help delay gastric emptying and delay the onset of hunger.[48] The addition of fiber to a meal can help modulate hunger signaling and therefore may be an important component in weight loss.[49]

2. ELIGIBILITY ASSESSMENT AND ENROLLMENT

We intend to test whether a high-legume intervention will result in increased satiety and in turn will facilitate reduced energy intake and weight loss compared to a control diet provided under similar conditions. We will recruit men at increased risk for colorectal cancer (see below) at two locations (1) Emory University ACTSI and (2) The Morehouse School of Medicine Medical Clinical Research Center Bionutrition Core Center (affiliated with the ACTSI) and surrounding areas. Participants will be recruited through targeted advertisements and (if approved) through targeted mailings with the assistance of local gastroenterologists serving these populations. These recruitment strategies were successfully used in our previous feeding trial which included 65 high risk men.

2.1. Eligibility Criteria

2.1.1. Inclusion Criteria

All subjects:

1. 40-70 years old
2. Male
3. BMI overweight-obese: 25.0—40 kg/m^2
4. Colonoscopy within the last three years that found ≥1 adenoma
5. English speaking
6. Ambulatory, able to come to either food distribution site to pick up food and participate in clinical examinations and laboratory tests

2.1.2 Exclusion Criteria

1. Serious medical condition (e.g., cancer, heart disease, kidney disease, diabetes)
2. History of CRC, bowel resection, polyposis syndrome, or inflammatory bowel disease
3. Smoked regularly in the past year
4. Dietary restrictions substantially limiting compliance or vegetarian or Vegan diet
5. Planning on changing diet or exercise behavior in the next 6 months
6. Regular use of medication that may alter inflammation markers, insulin, glucose, or gut function (i.e. regular use of non-steroidal anti-inflammatory medication, insulin therapy, steroid therapy, or antibiotics)

2.2. Research Eligibility Evaluation

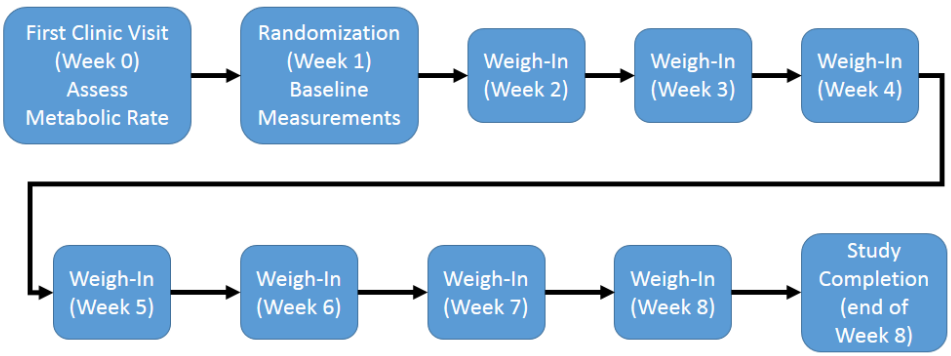
We will conduct the standard screening tests required by the ACTSI for healthy participants. A history and a physical will be performed by a clinician for all participants at the Emory ACTSI site (PA or Nurse Practitioner). Participants should be in good health. Use of medications to control blood pressure, blood lipids or other weight-related concerns is acceptable provided the participant is under a physician's care and considered in good control and the medication will not interfere with outcome measures.

2.2.1. Strategies to Recruit and Enroll Participants

Subjects eligible according to a phone interview will be invited to one of the study sites. On this visit, after receiving informed consent, the participant's height, weight, and blood pressure will be checked. All eligible consented participants will be asked to visit the Emory ACTSI site to assess their resting metabolic rate (RMR) to be used to plan meals that will facilitate a weight loss of 1-2 pounds per week (energy deficit ~500-1000 kcal/day). Once their individualized diet plan is developed participants will all undergo a one-week run-in of diet similar to the control diet. The run-in helps to standardize conditions before the baseline biomarker collection and provides some confidence in the participants' ability to adhere to the study protocol.

3. STUDY IMPLEMENTATION

Overall Study Design of Legume Pilot Trial



3.1.1. Timing of Biological Specimen Collection

At randomization, after a one week run-in period, the baseline blood and fecal samples will be collected. These same specimens will be also collected at the end of the study period, after 8 weeks. All biomarker collections will take place at the Emory ACTSI site.

3.1.2 Dietary Intervention Administration

A menu cycle will be developed with a standard set of legumes of the Phaseolus vulgaris species, such as navy beans, pinto beans, and kidney beans in order to limit nutrient and phytochemical differences in the legume-intervention diet. The diet will contain approximately 250g of legumes per day (~1 ½ cups cooked) provided in two pre-portioned single serving entrees (i.e. ~125g each). This level will add approximately 20 grams of total dietary fiber and 8 grams of soluble fiber per day. Adding 1 ½ cups of legumes would double the dietary fiber content of the typical American diet. The intervention diet treatment will consist of two legume-enriched pre-portioned meal entrees per day with other meal components being provided by the study participants. The control group will also receive two pre-portioned meal replacement entrees, with the other meal components provided by the study participants. All entrees will be prepared, pre-portioned and frozen at the Morehouse site and transported to the Emory site as needed. Frozen entrees will be picked up by participants weekly at the respective study sites and any uneaten entrees returned the following week and recorded. Weights will also be measured weekly at these visits. For both groups, guidance will be provided by study personnel for the meal components which are self-selected to meet participants' diet plans. Study personnel include three registered dietitians (the PI, a Co-I, and an ACTSI RD) to provide dietary guidance which will be supplemented with individualized written materials. During the first 1-2 weeks of the participants' diet treatment the study coordinator will contact them regularly to answer any questions and to provide support and encourage adherence. The consumption of ad libitum "sides" contributing to total energy intake is <u>not</u> controlled by the study to enable us to evaluate the role of legumes in promoting satiety and control of self-selected total food intake.

4. DATA COLLECTION AND EVALUTION

4.1 Data Collection

4.1.1 Anthropometric Measures

Body weight, height will be measured by trained personnel using procedures based on the NHANES Anthropometry Procedures Manual 63. Briefly, participants will have their body weight and height measured in light clothing without shoes on a regularly calibrated digital scale. Height will be measured in duplicate using a wall-mounted stadiometer.

4.1.2 Body Composition

Body composition will be assessed using dual energy X-ray absorptiometry (DXA) in the ACTSI at Emory University. This method uses a whole-body scanner to measure total body composition and fat content with a high degree of precision. It is safe and noninvasive with little burden to the individual. Data from the DXA scans will be used to assess longitudinal changes in body fat that accompany weight loss. This data will also allow examination of changes in fat distribution at defined regions in the body.

4.1.3. 24 Hour Diet Recall

Subjects will be asked by a trained study staff member to recall their food and beverage intake during the previous 24 hour period or the preceding day. During the week prior to randomization, two unannounced telephone 24 hour recall interviews will be conducted, one during a weekday and one on a weekend. This will be repeated again during the second week after randomization, and again during the 7th week of randomization. The interview will follow a four-stage, multiple-pass interview technique and be conducted over the phone using Nutrient Data Systems for Research (NDSR), the state of the art diet assessment and nutrient analysis

program for research. NDSR estimates total energy, macro- and micro-nutrient intake and captures intake for the entire day, specific meals, dietary patterns, or individual foods.

4.1.4. Satiety and Taste Measures

Meal Appetite Rating Forms will be provided to each subject to assess appetite and satiety in response to test meals for each diet treatment. These will be completed before the time course test meal, immediately after eating the test meal and each time blood is drawn. Increased hunger and decreased satiety have been linked to decreased adiposity and weight loss, and these changes may undermine the maintenance of weight loss[50-53].

A phone interview to assess participant satiety will be conducted two times a week for the duration of the study. These phone interviews will be performed separately from the 24 hour recall, and will be scheduled with participants in advance. This contact also will allow us to assess any gastrointestinal symptoms such as bloating, change in bowel habits and abdominal discomfort.

Two additional questionnaires will assess preferences for different types of foods and aspects of the two diets under standardized conditions. These two questionnaires will be administered twice during the study, baseline and follow-up.

4.1.5. Blood Collection

Approximately 70ml of blood will be collected from the subjects at each of two time points at randomization and at the end of the eight week diet period. Samples will be collected after an overnight fast and in the early morning. For satiety measures, 15 ml of blood will be drawn before the test meal (fasting), and 10 ml of blood at 5 time points thereafter (30, 60, 90, 120, and 180 minutes). Serum and plasma samples will be aliquoted in smaller vials and frozen at –70°C and stored for analysis at the completion of the study.

4.1.6. Blood Analyses

Approximately seventy microliters of serum will be used to measure insulin, glucose, total cholesterol, CCK and CRP using standard techniques.

4.1.7. Gastric Motility

The WMC system (SmartPill Corporation, Buffalo, NY) consists of an indigestible single-use capsule, a receiver, and display software (MotiliGI, SmartPill Corporation) recommended for the assessment of gastric emptying and gut transit time. Also included are assessments of pH, temperature and pressure through the GI tract. This series of studies will be conducted under the direction of gastroenterologist and co-investigator Dr. Jennifer Christie, Emory University.

After an overnight fast a representative study meal is consumed and immediately thereafter the participant swallows the SmartPill capsule with an additional 50 ml of water. The participant is then allowed to leave the facility. The participant will resume lunch 5 hours after capsule ingestion. During follow-up the participant records bowel movements, food intake sleep and any GI symptoms. The participant is asked to avoid strenuous exercise, alcohol, smoking and use of any medications that may affect GI motility. The data receiver and diary are returned after 5 days for analysis. Gastric emptying time, small bowel as well as colonic transit time can be estimated by the measuring changes in pH, pressure, and temperature. For example, the movement of the capsule from the stomach to the duodenum results in a pH rises of >3.[54]

4.1.8. Breath Hydrogen Test

Breath hydrogen tests will determine the amount of hydrogen (H_2) and methane (CH_4) present in expired breath following ingestion of a known volume of carbohydrate. The type of gas in expired breath depends on the type of bacteria present in the lower gut. Collection of a timed response will allow future calculation and determination of the amount of unabsorbed

carbohydrate in a meal through gut response measures. Breath hydrogen tests will be conducted at the same time as the time course experiments (insulin, glucose, CCK) and during the first day of the SmartPill testing. Collections are done at 30, 60, 90, 120, and 180 minutes after finishing the test meal, taken into a 30 cc syringe and sealed for later analysis in a Quintron Gas Analyzer.

4.1.9. Fecal Collection

Stool samples will be collected twice during the study, at the beginning and the end of the diet period. Subjects will be instructed in the use of a plastic device to cover the toilet seat and collect the stool. Two separate ~5 g samples will be taken for fecal microbiome analyses. All samples will be transported to the laboratory, coded by the research assistant, and held at –80° C for future microbiome analysis.

4.2. Statistical Considerations

The main endpoint of interest in this study is weight loss. There are several proposed mechanisms by which legumes are thought to promote weight loss, many of which have not been tested in a controlled setting. Due to new technology, we are now able to examine one of these proposed mechanisms—colon transit time, allowing us to directly observe a legume diet's physiologic effect. Previous studies of legume-heavy diets have shown indications that the particular type of fiber specific to legumes may increase satiety and slow gastric emptying significantly, leading patients to consume fewer calories per day, thereby promoting weight loss without intensive intervention from the study staff. Thus, we do expect to have differences in energy intake between groups. The analyses will follow the intent-to-treat principle. BMI will certainly be considered as a possible confounder. Since this is a pilot trial, doing so will be important to determine the appropriate target population for a full-scale trial and whether randomization in that protocol should be stratified by BMI. Secondary outcomes, including both the satiety hormones and glucose are expected to rise quickly in response to the test meal and then decline over the course of the next few hours as gastric emptying occurs.

In the Legume Inflammation Feeding Experiment full-feeding study, participants averaged -3.9 ± 0.4kg over the course of four weeks[8]. Ten participants (five individuals per treatment arm) would be sufficient to detect a difference of just 1.25kg (we expect > 1 kg) in weight loss, with 80% power, assuming a standard deviation for each groups' weight loss that is slightly higher (±0.7kg) than seen in our prior study[8]. To account for the potential small dropout rate, we will recruit a total of 14 patients (7 per treatment arm). There are multiple secondary outcomes that we are interested in determining the appropriate sample size for when we run a full-scale study. Some of these outcomes are novel, so we are exploring the feasibility of pursuing them in a full scale study.

Within-subject changes in end-points will be compared by paired t-test; comparisons between treatment groups by two-sample t-tests. For the time course experiments, because of the large expected individual variations in fasting levels of metabolic and appetite hormones, we intend to compute the change from baseline at each time point for each individual for all of the variables and subsequently comparing the area under the curve results[55]. All data will be presented as means ± SEM; the probability level at which differences will be considered significant will be $P<0.05$. All analyses will be performed using the most recent version of SAS (SAS Institute, Cary, NC).

Timeline

	Mo. 1	Mo. 2	Mo. 3	Mo. 4	Mo. 5	Mo. 6	Mo. 7	Mo. 8	Mo. 9	Mo. 10	Mo. 11	Mo. 12
IRB Approval, set up	X	X										
Recruiting			X	X	X	X	X	X				
Follow-up				X	X	X	X	X	X	X		
Biomarker Analysis									X	X	X	X
Statistical Analysis											X	X
Manuscript Preparation											X	X
Report to Funding Agency												X
Draft of Subsequent R01												X

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