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ORIGINAL ARTICLE

Clinical Trials and Investigations

High- and normal-protein diets improve body composition and glucose control in adults with type 2 diabetes: a randomized trial

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The Beef Checkoff

Abstract

Objective: Weight loss of ≥10% improves glucose control and may remit type 2 diabetes (T2D). High-protein (HP) diets are commonly used for weight loss, but whether protein sources, especially red meat, impact weight loss-induced T2D management is unknown. This trial compared an HP diet including beef and a normal-protein (NP) diet without red meat for weight loss, body composition changes, and glucose control in individuals with T2D.

Methods: A total of 106 adults (80 female) with T2D consumed an HP (40% protein) diet with ≥4 weekly servings of lean beef or an NP (21% protein) diet excluding red meat during a 52-week weight loss intervention. Body weight, body composition, and cardiometabolic parameters were measured before and after intervention.

Results: Weight loss was not different between the HP (−10.2 ± 1.6 kg) and NP (−12.7 ± 4.8 kg, $p = 0.336$) groups. Both groups reduced fat mass and increased fat-free mass percent. Hemoglobin A1c, glucose, insulin, insulin resistance, blood pressure, and triglycerides improved, with no differences between groups.

Conclusions: The lack of observed effects of dietary protein and red meat consumption on weight loss and improved cardiometabolic health suggests that achieved weight loss, rather than diet composition, should be the principal target of dietary interventions for T2D management.

INTRODUCTION

Type 2 diabetes (T2D) affects more than 30 million adults in the United States and presents numerous public health challenges [1]. T2D is a major risk factor for cardiovascular disease [2], kidney disease [3, 4], amputation [5–7], certain cancers [8], and blindness [9, 10], which result in a major cost burden to the health care system [1]. The primary risk factor for T2D is obesity, with the majority of those with T2D having overweight or obesity [11, 12]. Obesity also increases the risk of several other comorbid conditions, including heart disease and stroke [11, 13, 14]. It has been demonstrated that both T2D and obesity can be treated with lifestyle modification. For example, in Diabetes Remission Clinical Trial (DiRECT), weight loss of 10 to 15 kg resulted in the remission of T2D in a majority of individuals who had been diagnosed with T2D within the past 6 years. Nearly nine in ten of individuals achieving more than 15 kg of weight loss remitted their T2D [15]. Although it is clear that weight loss is associated with improvements in T2D, the role of diet composition in the reversal of T2D presents a gap in knowledge.

Higher protein diets are an attractive target for lifestyle-based interventions for the treatment of T2D. High-protein (HP) diets, especially when combined with exercise, produce greater weight loss and prevent loss of fat-free mass (FFM) compared with lower protein diets [16–18]. In premenopausal women with obesity but without diabetes, an HP diet improved insulin sensitivity more than a high-carbohydrate diet, even though achieved weight loss was not different between diets (HP: 9.8% ± 1.4%, high-carbohydrate: 9.3% ± 1.6%, $p = 0.9323$) [19]. Conversely, a study in postmenopausal women found that consuming an HP diet during weight loss eliminated the beneficial effects of 10% weight loss on insulin action and sensitivity [20]. These conflicting results suggest that additional studies on the amount and sources of dietary protein during weight loss are needed to determine the influence on weight loss-induced improvements in T2D.

Red meat, and beef in particular, is an important contributor to dietary protein intakes in the United States [21]. However, some observational studies have associated red meat consumption with higher risk of T2D, leading to recommendations to limit its consumption [22, 23]. Recommendations to limit red meat consumption are based mostly on observational data, whereas findings from randomized clinical trials usually have found a neutral effect of red meat consumption on health outcomes [24–28]. A recent meta-analysis found no differences in most glycemic and insulinemic risk factors associated with T2D when comparing reduced or no red meat diets with diets that contained red meat [29]. However, the impact on red meat consumption during weight loss among people with T2D remains ambiguous. Therefore, it would be important to know whether beef can be part of an HP dietary plan to reverse T2D by contributing to weight and fat loss and improving weight loss maintenance.

The purpose of this randomized clinical trial was to compare an HP versus a normal-protein (NP) diet for weight loss, body composition changes, and indicators of T2D status during a 52-week behavioral weight loss intervention. Both intervention diets were energy-restricted, and the HP diet included recommendations to include lean beef in the diet, whereas participants in the NP diet group were instructed to refrain from eating any red meat for the duration of the study. The hypotheses were that the HP diet would lead to greater weight loss, preferential loss of fat mass compared with FFM, and greater improvements in glucose control and cardiometabolic health.

Study Importance

What is already known?

- Weight loss of ≥10% improves glucose control and can even remit type 2 diabetes (T2D) for some.
- High-protein diets can produce greater weight loss and prevent loss of fat-free mass compared with diets lower in protein.
- Some observational studies have recommended limiting red meat consumption to reduce risk for T2D, but data from randomized clinical trials generally find little to no independent effect of lean red meat consumption.

What does this study add?

- Both a normal-protein diet excluding red meat and a high-protein diet containing minimally processed lean beef are effective at producing weight loss and improvements in glucose control.

How might these results change the direction of research or the focus of clinical practice?

- Weight loss, not diet composition, is the primary driver of T2D management.
- Avoiding red meat, including beef, does not provide additional benefit for weight loss or improvements in glucose control during a weight loss intervention.

METHODS

Participants

A total of 106 individuals (80 female individuals) began the intervention and were recruited from the Denver, Colorado ($n = 39$) and Birmingham, Alabama ($n = 67$) metropolitan areas using letters, internet advertisements, and news advertisements to participate in the trial. A diagram depicting participant flow is presented in Figure 1. The study was conducted in three cohorts, with approximately 35 participants in each cohort. Cohort 1 was from the Denver area and these participants began the intervention in January 2020. Cohorts 2 and 3 were from the Birmingham area and these participants began in February 2020 and April 2021, respectively. Participants were required to be at least 18 years old, have BMI ≥ 27 kg/m^2, have had a T2D diagnosis within the past 6 years (documented physician diagnosis, fasting glucose ≥ 126 mg/dL, or hemoglobin A1c [HbA1c] ≥ 6.5%), be weight stable (±3 kg in the past 3 months), and be stable on all medications for the past 3 months. Regarding eligibility criteria for T2D diagnosis, participants enrolled were those who had a recent diagnosis as described earlier without meeting the threshold for fasting glucose or HbA1c if that participant was on medication to manage T2D, which would lower these values. Exclusion criteria were as follows: HbA1c ≥ 12%; current eating disorder (anorexia or bulimia); dependence on illicit drugs or alcohol; untreated hypothyroidism; currently using insulin or other drugs known to cause weight loss or gain (including glucagon-like peptide-1 or sodium/glucose cotransporter 2 medications, steroids, tricyclic antidepressants, chemotherapy, antipsychotics, or prescribed or over-the-counter weight loss agent); following a vegetarian or vegan diet; any illness or injury that would make it unsafe to follow a diet and/or exercise up to 70 minutes at a moderate intensity regularly; and women who were pregnant, lactating, trying to become pregnant, or who had been pregnant or lactating in the last 6 months. Criteria for diabetes diagnoses were confirmed through medical records or doctor reports, blood biomarkers were

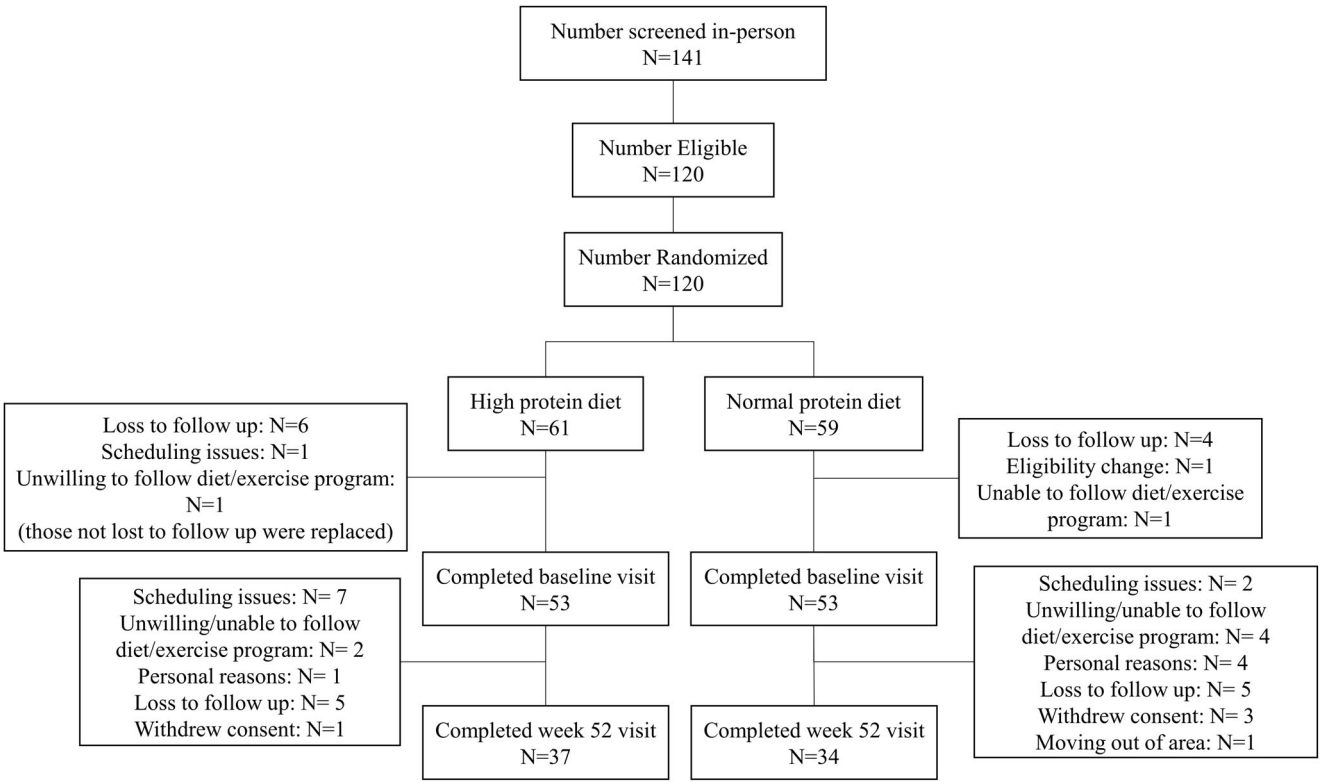

FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) diagram of participant flow

confirmed via a blood test at the screening visit, and all other criteria were confirmed by self-report. The study protocol was reviewed and approved by the Institutional Review Boards at the University of Alabama at Birmingham and the University of Colorado Anschutz Medical Campus. The study was registered on ClinicalTrials.gov as NCT03832933.

Experimental design

All participants followed the State of Slim (SOS) weight management program for the first 16 weeks of the program, which consisted of weekly group classes led by a trained coach. Participants received copies of the SOS book, copies of the course materials, and access to the online community. After the first 16 weeks, participants participated in the SOS Next Steps program, which consists of 18 biweekly group classes for the remainder of the intervention. Participants were randomly assigned to one of two diet groups: the HP group, with instructions to consume ≥4 weekly servings of lean beef as the only source of red meat; or the NP group, with instructions to not eat red meat for the duration of the study and to follow a modified SOS diet that reduced protein intake.

Diet intervention

The SOS plan is broken up into three distinct phases, each of which has food lists for participants to choose from as well as defined portion sizes for each food. Typically, the SOS plan is a high-protein, low-fat diet plan that emphasizes nonstarchy and whole-grain carbohydrates. The SOS plan also has five diet rules that are to be followed throughout each phase: 1) Eat five to six times per day; 2) Eat breakfast within 1 hour of waking; 3) Do not count calories and, instead, measure portions; 4) Have the right protein mix at each meal (one carbohydrate and one protein at each meal); and 5) Eat a healthy fat twice a day. Food lists for the HP and NP groups were similar, with the exception of the HP group being asked to consume lean beef ≥4 times per week and the portion sizes for protein being reduced for the NP group. Approximate carbohydrate and protein compositions were 32% and 40% of total energy for the HP diet, respectively, and 53% and 21% for the NP diet, respectively. Recommended fat intakes were similar for the HP (28% of total energy) and NP (26%) groups. Food lists for each phase given to participants with adjusted portion sizes are presented in Supporting Information Tables S1 through S3. In addition, participants worked up to exercising up to 70 minutes per day, 6 days per week as a part of the program.

Self-reported energy intake and macronutrient distribution were not tracked during the study because a principal component of the SOS program is to focus on portion sizes as opposed to counting calories (Diet Rule #3). Participants did complete food logs throughout the intervention; however, these were used as a self-monitoring tool to enhance weight loss [30] and were not intended to measure energy intake or macronutrient distribution. Per the diet rules, a detailed food log designed to capture these

data would be inconsistent with the program goals and structure. Furthermore, self-reported measurements of food intake are unreliable, and their suitability for clinical research has been questioned [31].

Participants were instructed that clinical decision-making in regard to T2D management was to be made with their primary care provider, but participants were asked to report any medication changes to research staff as soon as feasible. Study staff also queried participants on any medication changes on a monthly basis throughout the study period.

Protocol modifications due to COVID-19

The original plan for this intervention was for SOS classes to be held in person. The onset of lockdown orders in the spring of 2020 due to the COVID-19 pandemic required that classes be moved to an online platform (Zoom). The online intervention format was used for the remainder of the trial. The group classes were switched to the online format for cohort 1 (Colorado) at week 7 of the intervention and at week 4 for cohort 2 (Alabama). The intervention for cohort 3 (Alabama) was conducted entirely online. Weekly self-weighing was completed at home, with pictures of scale weights sent to the health coaches in lieu of weighing in person before each class. Additionally, the week 16 study visits became at-home study visits for cohorts 1 and 2 with limited data collection due to university-wide restrictions on in-person clinical research at the University of Colorado Anschutz Medical Campus and the University of Alabama at Birmingham. Participants were sent a link to a video call with research staff who conducted the visit. For this manuscript, baseline and week 52 data were used to assess study outcomes because of the limited data collection techniques used during the week 16 visits.

Anthropometric measurements

Body weight was measured at baseline and week 52 using a digital platform scale (Colorado: Tanita BWB-800, Tanita Cooperation of America, Inc.; Alabama: DETECTO BRW1000) in a fasted state in the clinic, with participants wearing light clothing after voiding. Height was measured using a stadiometer in the clinic at the screening visit. Body mass index (BMI, weight in kilograms divided by height in meters squared) was calculated using these measurements. Body composition (fat and lean mass) was measured using dual x-ray absorptiometry at baseline and week 52 (Colorado: Horizon W, APEX software version 5.6.05 Hologic, Inc.; Alabama: GE Lunar Prodigy Primo, enCORE software version 15.10.046, GE Healthcare). Waist circumference (WC) was measured at the border of the iliac crest in duplicate, in accordance with the National Institutes of Health recommendations [32], at baseline and week 52.

TABLE 1 Baseline characteristics of participants

Parameter	HP	NP
Age (y), M ± SD	54.1 ± 12.0	55.4 ± 9.6
Duration of T2D (y), M ± SD	3.2 ± 1.8	3.2 ± 1.6
Female, *n* (%)	38 (72)	42 (79)
Using medications for T2D, *n* (%)	48 (91)	46 (87)
Anthropometrics, M ± SD		
Weight (kg)	108.0 ± 22.8	107.8 ± 26.6
BMI (kg/m^2)	38.7 ± 6.8	38.8 ± 7.3
WC (cm)	118 ± 14	117 ± 15
Fat mass (%)	46.2 ± 6.2	46.6 ± 5.9
FFM (%)	52.9 ± 6.1	52.4 ± 5.8
Biomarkers, M ± SD		
HOMA-IR	7.6 ± 7.0	5.9 ± 3.4
Glucose (mg/dL)	134 ± 38	130 ± 40
HbA1c (%)	7.2 ± 1.0	7.0 ± 1.3
Insulin (μIU/mL)	22.3 ± 16.5	18.1 ± 11.1
BP systolic (mm Hg)	135 ± 15	135 ± 15
BP diastolic (mm Hg)	86 ± 9	86 ± 9
Triglycerides (mg/dL)	138 ± 71	139 ± 58
HDL cholesterol (mg/dL)	47 ± 11	45 ± 9
LDL cholesterol (mg/dL)	94 ± 28	95 ± 36
Race, *n* (%)		
White	37 (70)	30 (57)
Black	11 (21)	19 (39)
Asian	3 (6)	1 (2)
Native Hawaiian or Pacific Islander	1 (2)	0 (0)
Other	1 (2)	3 (6)
Ethnicity, *n* (%)		
Hispanic	6 (11)	9 (17)
Non-Hispanic	46 (87)	43 (81)
Did not report	1 (2)	1 (2)

Note: Percent of sample (i.e., percent female, percent using medications for T2D), WC, and blood biomarkers rounded to the nearest whole number (except HOMA-IR, HbA1c percent, and insulin).
Abbreviations: BP, blood pressure; FFM, fat-free mass; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; HP, high-protein; LDL, low-density lipoprotein; M, mean; NP, normal-protein; T2D, type 2 diabetes; WC, waist circumference.

Cardiometabolic health

Blood samples were obtained at baseline and week 52 from an antecubital vein by a trained phlebotomist. Samples were processed and analyzed for glucose, total cholesterol, low-density lipoprotein cholesterol (LDL; calculated), high-density lipoprotein cholesterol (HDL), triglycerides, HbA1c, and blood urea nitrogen (BUN). Blood samples were processed at the University of Alabama Outreach Lab for

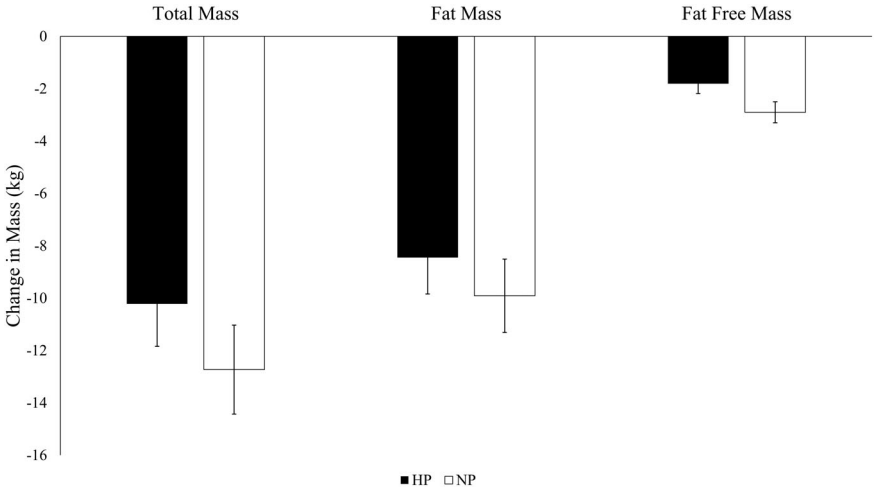

FIGURE 2 Change in body weight and composition (fat and FFM) in kilograms from baseline to week 52 by diet group. Mixed-effects models used to test the effect of diet group, time, and their interaction term on body weight and composition changes. Presented as least-squares means ± SE. Both groups had significantly reduced weight (HP, −10.2 ± 1.6 kg; NP, −12.5 ± 1.6 kg), fat mass (HP, −8.4 ± 1.4 kg; NP, −9.1 ± 1.5 kg), and FFM (HP, −1.8 ± 0.4 kg; NP, −2.9 ± 0.4 kg), but the majority of weight loss was due to fat mass loss. There were no differences in outcomes by diet group in changes in total mass ($p = 0.333$), fat mass ($p = 0.735$), or FFM ($p = 0.056$). FFM, fat-free mass; HP, high-protein; NP, normal-protein

TABLE 2 Changes in indicators of T2D by diet group

Parameter	Group	Baseline	Week 52	Mean change	95% CI for change	*p* value
Glucose (mg/dL)	HP	134 (5)	115 (6)	−19 (6)	(−31.0 to −6.8)	
	NP	130 (5)	111 (6)	−19 (6)	(−31.4 to −6.4)	0.999
HbA1c (%)	HP	7.2 (0.2)	6.4 (0.2)	−0.8 (0.2)	(−1.1 to −0.4)	
	NP	7.0 (0.2)	6.5 (0.2)	−0.5 (0.2)	(−0.9 to −0.1)	0.329
Insulin (μIU/mL)	HP	22.3 (1.9)	14.5 (1.7)	−7.8 (2.0)	(−11.8 to −3.7)	
	NP	18.8 (1.9)	11.0 (1.8)	−7.8 (2.0)	(−12.0 to −3.7)	0.979
HOMA-IR	HP	7.6 (0.8)	4.5 (0.7)	−3.1 (0.8)	(−4.7 to −1.6)	
	NP	5.9 (0.8)	3.2 (0.7)	−2.7 (0.8)	(−4.2 to −1.1)	0.657

Note: Values presented as least-squares means (SE) with glucose values rounded to nearest whole number. Values are model based from the intention-to-treat analysis performed, including least-squares means, change, and 95% CI. *P* value represents differences in change between diet groups (HP vs. NP). Mixed-effects model used to test the effect of time, group, and their interaction term on changes in indicators of T2D. Both diet groups reduced glucose, HbA1c, insulin, and HOMA-IR from baseline to week 52. There were no differences in change in any parameters by diet group (HP vs. NP).
Abbreviations: HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; HP, high-protein; NP, normal-protein; T2D, type 2 diabetes.

Alabama samples and at the University of Colorado Hospital Clinical Lab for screening and the Adult Clinical and Translational Research Centers (CTRC) Core lab for baseline and week 52 visits for Colorado samples. Blood pressure was measured at each in-person study visit at the left upper arm using an automatic sphygmomanometer (Colorado: Datascope Trio [Serial# MC07547-A5], Mindray; Alabama, Omron 3-Series Upper Arm Blood Pressure Monitor, OMRON Healthcare Inc.). Blood pressure was measured after the participant rested quietly in a seated position for ≥5 minutes, with participants' legs uncrossed and back and arms supported. The measurement was taken two times, and if the reading differed by more than 5 mm Hg, a third measurement was obtained.

Statistical analyses

All study data were collected and managed using REDCap electronic data capture tools hosted at the University of Alabama at Birmingham and University of Colorado Denver [33, 34]. REDCap is a secure, Web-based software platform designed to support data capture for research studies, providing the following: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. All analyses were completed using SAS (version 9.4, 2002–2012 by SAS Institute Inc.).

A sample size of 120 participants was targeted based on findings from the Beef WISE (weight improvement, satisfaction, and energy) Study [25] to detect a 2.75-kg difference in weight loss between the HP and NP groups. Weight loss achieved by the "Beef" group in the Beef WISE Study was 8.9 ± 6.0 kg, and this group received the same dietary plan and counseling as the HP group in the current study. Assuming a similar amount and variability in achieved weight loss, statistical power calculations indicated that a sample size of 112 (56 per group) would provide >80% power ($\alpha = 0.05$) to detect a 2.75-kg difference in weight loss.

Baseline characteristics were assessed by diet group (HP and NP), as well as the total of the whole sample. Randomization was performed by the statistician and was stratified by age, sex, BMI, and years since diagnosis of T2D. Differences in baseline characteristics were assessed using paired *t* tests or χ^2 tests. Linear mixed models with unstructured covariance were used to test the effect of diet group, time, and their interaction term for changes in body weight and composition and cardiometabolic health using an intention-to-treat approach, meaning that all participants who were randomized and who had one or more measures were included in linear mixed-model analyses, regardless of completion of protocol or adherence. Differences in frequency of reducing or discontinuing medication for T2D were assessed using χ^2 tests. $P < 0.05$ was deemed statistically significant.

TABLE 3 Changes in T2D status

	HP, *n* (%)	NP, *n* (%)
ITT approach		
Remained in abnormal range	7 (13)	12 (23)
Remained in normal range	12 (19)	9 (17)
Positive change (abnormal to normal value)	13 (25)	12 (23)
Negative change (normal to abnormal)	4 (8)	1 (2)
Unknown (no paired value)	19 (36)	16 (30)
Completers analysis		
Remained in abnormal range	7 (21)	12 (33)
Remained in normal range	10 (2)	9 (25)
Positive change (abnormal to normal value)	13 (38)	14 (39)
Negative change (normal to abnormal)	4 (12)	1 (3)

Note: Changes in status of T2D as indicated by HbA1c ≥ 6.5% or fasting glucose ≥ 126 mg/dL (clinically diagnostic of T2D) from baseline to week 52 of the trial. Unknown in the ITT approach refers to participants without either a baseline or week 52 value; therefore, no conclusions could be made regarding change in status. Abnormal value refers to lab values consistent with T2D diagnosis where normal range refers to values below the criteria for T2D diagnosis. Percents rounded to nearest whole number.
Abbreviations: HP, high-protein; ITT, intention-to-treat; NP, normal-protein; T2D, type 2 diabetes.

RESULTS

Baseline characteristics of participants

Baseline characteristics of participants are presented in Table 1. No differences in any baseline characteristics were detected between the HP and NP groups. Participant retention at 52 weeks did not differ

TABLE 4 Laboratory marker changes by diet group

Parameter	Group	Baseline	Week 52	Mean change	95% CI for change	*p* value
BP systolic (mm Hg)	HP	135 (2)	126 (3)	−9 (2)	(−13.0 to −5.1)	
	NP	135 (2)	127 (3)	−8 (2)	(−12.2 to −3.9)	0.719
BP diastolic (mm Hg)	HP	86 (1)	78 (1)	−7 (2)	(−10.2 to −4.2)	
	NP	86 (1)	81 (2)	−6 (2)	(−8.6 to −2.3)	0.430
Triglycerides (mg/dL)	HP	138 (9)	114 (10)	−25 (9)	(−42.8 to −6.1)	
	NP	139 (9)	110 (10)	−29 (10)	(−48.0 to −10.0)	0.732
HDL cholesterol (mg/dL)	HP	47 (1)	47 (2)	2 (1)	(−2.1 to 2.9)	
	NP	45 (1)	47 (2)	1 (2)	(−0.8 to 4.4)	0.448
LDL cholesterol (mg/dL)	HP	94 (4)	91 (5)	−3 (4)	(−11.1 to 4.6)	
	NP	95 (4)	94 (5)	−1 (4)	(−9.3 to 6.9)	0.718
BUN	HP	15 (1)	17 (1)	3 (1)	(1.5 to 4.2)	
	NP	15 (6)	18 (1)	3 (1)	(1.2 to 4.0)	0.770

Note: Values presented as least-squares means (SE) rounded to the nearest whole number. Values are model based from the intention-to-treat analysis performed, including least-squares means, change, and 95% CI. *P* value represents differences in change between diet groups (HP vs. NP). Mixed-effects model used to test the effect of time, group, and their interaction term on changes in laboratory markers. Both diet groups reduced systolic and diastolic BP and triglycerides from baseline to week 52. Neither group had changes in HDL or LDL cholesterol from baseline to week 52. Both groups increased BUN from baseline to week 52. There were no differences in change in any parameters by diet group (HP vs. NP).
Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; HDL, high-density lipoprotein; HP, high-protein; LDL, low-density lipoprotein; NP, normal-protein.

between the HP and NP groups (completed: HP, $n = 37$ [69.8%]; NP, $n = 34$ [64.2%], $p = 0.51$).

Adverse events

No adverse events likely to be related to the study were reported by participants in either group.

Weight loss and body composition

Changes in body weight and composition are shown in Figure 2. Total mass was reduced by 10.2 ± 1.6 kg (9.4%) in the HP group and 12.7 ± 4.8 kg (11.8%) in the NP group (Figure 2), with no differences between groups ($p = 0.336$). Fat mass percent decreased (HP, 46.2% ± 0.8% vs. 41.9% ± 1.1%, $p < 0.001$; NP, 46.6% ± 0.8% vs. 42.8% ± 1.6%, $p < 0.001$) and FFM percent increased (HP, 52.9% ± 0.8% vs. 57.1% ± 1.1%, $p < 0.001$; NP, 51.8% ± 1.6%, vs. 55.4% ± 0.8%, $p < 0.001$) in both groups during the intervention period, with no significant differences between the HP and NP groups (fat mass percent, $p = 0.665$; FFM percent, $p = 0.689$). Both the HP and NP groups reduced WC (HP, 118 ± 2 cm vs. 111 ± 2 cm, $p \leq 0.001$; NP, 117 ± 2 cm vs. 109 ± 2 cm, $p \leq 0.001$) and BMI (HP, 38.7 ± 1.0 kg/m^2 vs. 35.0 ± 1.0 kg/m^2, $p \leq 0.001$; NP, 38.8 ± 1.0 kg/m^2 vs. 34.4 ± 1.0 kg/m^2, $p \leq 0.001$) from baseline to week 52, with no differences between groups (WC, $p = 0.934$; BMI, $p = 0.421$). Supporting Information Figure S1 includes additional plots related to body composition changes by group.

Indicators of T2D

Changes in indicators of T2D are presented in Table 2. In general, participants reduced HbA1c, fasting glucose, and homeostatic model assessment for insulin resistance, with no differences in changes between the HP and NP groups. Data describing participants with HbA1c ≥ 6.5% or fasting glucose ≥ 126 mg/dL (clinically diagnostic of T2D) at baseline and week 52 by diet group are presented in Table 3. At baseline, 73.6% of participants in the HP group and 62.3% of participants in the NP group had biomarkers in the range for T2D. Using the intention-to-treat approach, 24.5% and 22.6% of participants in the HP and NP groups, respectively, reduced these values to no longer meet diagnostic criteria for T2D. Using the completer analyses, these numbers are 38.2% and 38.5% for the HP and NP groups, respectively. Four participants in the HP group and one participant in the NP group were classified as having a negative change, with values at baseline not meeting criteria for T2D diagnosis but meeting these criteria at week 52. There were no differences between diet groups for any changes in T2D indicators. In addition, during the trial, $n = 14$ participants (HP, $n = 5$; NP, $n = 9$) discontinued all T2D medications, and $n = 16$ (HP, $n = 7$; NP, $n = 9$) reduced at least one T2D medication. The frequency of discontinuing or reducing T2D medications was not statistically different between the HP and NP groups ($p = 0.4358$).

Laboratory markers

Changes in blood pressure, lipids, and BUN are summarized in Table 4. Participants reduced systolic and diastolic blood pressures and triglycerides, with no differences between groups. BUN was increased in both groups at week 52 compared with baseline, with no differences between the HP and NP groups. There were no changes in total cholesterol, HDL cholesterol, or LDL cholesterol in either group over the duration of the intervention.

DISCUSSION

Both the HP and NP diet groups significantly reduced weight and improved in key indicators of T2D, with no differences between groups. These findings support data suggesting that weight loss is the primary driver of improvements in glucose control. Results from the Look AHEAD (Action for Health in Diabetes) study found that those with a 5% to 10% reduction in weight had increased odds of achieving a 0.5% reduction in HbA1c (odds ratio 3.52) [35]. Evidence from review papers has also suggested that modest weight loss can successfully result in remission of T2D in many individuals [36]. Findings from the current study further support the notion that weight loss can produce improvements in glucose control in many with T2D. Average weight loss in the current study was consistent with that found to cause improvements in T2D in the majority of participants in DiRECT [15]. Our results extend those of previous research by demonstrating that weight loss is an effective treatment for T2D.

Contrary to the hypothesis, the HP diet did not result in greater weight loss when compared with the NP diet. Instead, the groups had similar weight loss and body composition changes following the intervention. It was also hypothesized that the HP group would result in preferential loss of fat mass compared with FFM, which was also not supported. A recent review suggested that weight loss could increase the risk of mortality for those recently diagnosed with T2D, potentially as a result of a decline in appendicular lean mass [37]. Although appendicular body composition was not analyzed for the present study, whole-body FFM was only slightly reduced, with no significant differences between groups. The preferential loss of fat mass in both diet groups in the present study lessens concerns related to potential weight loss-related adverse events.

Results from this study also add to the literature regarding the impact of HP diets during weight loss for individuals with T2D. The HP and NP groups had similar reductions in indices of T2D, including HbA1c and fasting glucose. Some trials have demonstrated that an HP diet is more beneficial than a high-carbohydrate diet in outcomes associated with T2D [19, 38]. However, one trial in postmenopausal women demonstrated that an HP diet during weight loss could negatively impact insulin action [20]; however, this did not seem to be the

case in the present study, as marked by similar improvements in homeostatic model assessment for insulin resistance across groups. In the present study, at baseline, 73.6% of participants in the HP group and 62.3% of participants in the NP group had biomarkers in the range for T2D. Notably, inclusion in the study was based on previously diagnosed T2D but it did not require participants to present with a diagnostic value for HbA1c or fasting glucose at baseline. This resulted in some participants having HbA1c or fasting glucose below the diabetic range at study entry. This is likely because many participants were taking T2D medications at baseline, and they were not required to discontinue medications at study entry, as has been done in other studies such as DiRECT [15]. The percentage of participants exhibiting indices of T2D was reduced to 35.1% and 32.4% in the HP and NP groups, respectively. These findings strongly suggest that achieved weight loss, regardless of dietary pattern, is the primary factor driving improvements in glucose control. This finding has substantial public health implications because it provides a degree of individual-level flexibility in choosing a dietary pattern that is consistent with patient preferences.

These results demonstrate that the inclusion of minimally processed lean beef does not impact the effectiveness of an energy-restricted diet to induce weight loss and improvements in cardiometabolic health. Previous work from our group found equivalent changes in body weight and composition between an HP diet including beef and an HP diet excluding all red meat [25]. The present study builds on this work through the investigation of two diets with differing recommended macronutrient compositions. From these data, it is evident that minimally processed lean beef can be safely included in diets when attempting to lose weight and control glucose.

A limitation of this trial was that, despite giving explicit diet rules and lists to participants, both groups saw an increase in BUN from baseline to week 52. This finding could indicate that the protein composition of the diet groups likely did not reach the intended macronutrient distributions, with the groups consuming similar amounts of protein. The study might not have been able to detect the true impact on improvements in T2D markers because participants discontinued medications as recommended by their primary care providers. This could mean that the observed intervention could have had a greater effect if those participants had stayed on their medications. Additionally, the COVID-19 pandemic began during the first cohort of the Alabama and Colorado groups and lasted throughout the rest of the study. The onset of the pandemic resulted in several methodological changes to the study and impacted the lives of participants taking part in the intervention. Fortunately, the SOS program had been previously delivered in a virtual format; therefore, changes to course content were minor. Classes were still able to be held at the usual time, but in a virtual setting. However, research study visits were completely halted for a period during the study; therefore, the completion of some of the week 16 visits happened virtually instead of in person. This change limited the data that could be collected at this time point. In addition, some outcome measurement tests that were originally collected in person could no longer be collected at all, even when restrictions were lifted, including resting energy expenditure and a 6-minute walk test. These two tests were removed because masks were still required in the research facility, and, because baseline measurements were collected without masks, it was unclear whether the use of masks at future visits would impact results. Some participants who withdrew from the study cited COVID-19 as a primary reason for leaving, such as increased work demands. Total attrition overall was high, at 33%, which is likely to the challenges faced during the COVID-19 pandemic. Despite challenges, the study team was able to adapt swiftly to the nature of the pandemic and continue the intervention and data collection.

These results show that behavioral weight loss programs can produce significant weight loss in those with T2D, and that this weight loss can improve glucose control and many other aspects of cardiometabolic health. Results also show that avoiding red meat does not provide an advantage either in weight loss or in disease management.O

AUTHOR CONTRIBUTIONS

James O. Hill, Holly R. Wyatt, and R. Drew Sayer conceived the research project; Julianne G. Clina and Caroline W. Cohen conducted the research; Zhaoxing Pan performed the statistical analyses; Julianne G. Clina drafted the manuscript, and R. Drew Sayer, James O. Hill, Holly R. Wyatt, Caroline W. Cohen, Michael T. McDermott, Victoria A. Catenacci, and Zhaoxing Pan provided critical feedback and edits to the manuscript. All authors take responsibility for the final content of the manuscript.

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CONFLICT OF INTEREST STATEMENT

James O. Hill and Holly R. Wyatt have received royalties from the book *State of Slim: Fix Your Metabolism and Drop 20 Pounds in 8 Weeks on the Colorado Diet*. They have ownership in Shakabuku LLC, which offers weight loss to the public. Holly R. Wyatt has received grant support for unrelated studies from Gelesis, Novo Nordisk A/S, Epitomee, and General Mills, Inc.; has done consulting for Gelesis; and reports speaking fees from Novo Nordisk A/S and the National Cattlemen's Beef Association. James O. Hill has received grant funding for unrelated studies from Gelesis and has done consulting for Gelesis, General Mills, Inc., and McCormick Science Institute. R. Drew Sayer has received grant support for an unrelated study from General Mills, Inc., and reports speaking fees from the Texas Beef Council. The other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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