

A plant-based, low-fat diet decreases *ad libitum* energy intake compared to an animal-based, ketogenic diet: An inpatient randomized controlled trial

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Abstract

Competing models of obesity and its treatment often contrast the relative roles of dietary fat versus carbohydrate. Advocates of low-carbohydrate diets posit that intake of high glycemic carbohydrates leads to elevated postprandial insulin thereby promoting body fat accumulation while increasing hunger and energy intake according to the carbohydrate-insulin model of obesity. Alternatively, proponents of low-fat diets argue that high fat intake promotes body fat storage due to passive overconsumption of energy resulting from the high energy density of dietary fat. To test these competing models, 20 adults without diabetes aged (mean \pm SE) 29.9 \pm 1.4 y with BMI=27.8 \pm 1.3 kg/m² were admitted as inpatients to the NIH Clinical Center and randomized to consume *ad libitum* either a plant-based, low-fat (PBLF) diet (75.2% carbohydrate, 10.3% fat, non-beverage energy density = 1.1 kcal/g) or an animal-based, ketogenic, low-carbohydrate (ABLC) diet (75.8% fat, 10.0% carbohydrate, non-beverage energy density = 2.2 kcal/g) for two weeks followed immediately by the alternate diet for two weeks. Three daily meals plus snacks amounting to twice each subject's estimated energy requirements were provided and subjects were instructed to eat as much or as little as desired. The PBLF diet resulted in substantially greater glucose and insulin levels whereas the ABLC diet led to increased blood ketones of ~3 mM which is thought to suppress appetite. However, *ad libitum* energy intake was 689 \pm 73 kcal/d lower during the PBLF diet as compared to the ABLC diet ($p<0.0001$) with no significant differences in appetite ratings or enjoyment of meals. These data challenge the veracity of the carbohydrate-insulin model of obesity and suggest that the PBLF diet had benefits for appetite control whereas the ABLC diet had benefits for lowering blood glucose and insulin.

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Introduction

Changes in the food environment are thought to have caused increasing obesity prevalence over the past several decades¹, but there is considerable debate about which changes are most responsible for promoting excess energy intake. Two competing models of obesity and its treatment contrast the relative roles of dietary fat versus carbohydrate. Advocates of low-carbohydrate diets posit that intake of diets with high glycemic carbohydrates results in elevated postprandial insulin thereby promoting body fat accumulation while increasing hunger and energy intake^{2,3}. Alternatively, proponents of low-fat diets argue that high fat foods promote passive overconsumption of energy due to their weak effect on satiation, satiety, and their high energy density⁴⁻⁶.

Whether consumption of a low-carbohydrate or a low-fat diet offers benefits for appetite control thereby moderating energy intake has been the subject of long-standing debate. Outpatient diet studies have repeatedly failed to observe meaningful differences in long-term weight loss when subjects are randomized to follow low-carbohydrate versus low-fat diet prescriptions⁷. However, free-living subjects often fail to adhere to the prescribed diets, even when all study food is provided^{8,9}. Furthermore, neither food intake nor diet adherence can be adequately assessed with self-reported food intake measurements used in outpatient diet studies¹⁰⁻¹³. Therefore, inpatient studies are required to precisely control and accurately measure food intake¹⁴.

Few previous inpatient diet studies lasting more than a few days have measured *ad libitum* intake differences between diets varying in carbohydrate and fat¹⁵⁻¹⁷ and none have investigated exemplary low-carbohydrate versus low-fat diets that were both sufficiently low in their targeted macronutrients to potentially reveal the benefits of one diet over another.

For example, substantial restriction of dietary carbohydrate is required to induce a state of ketosis that is thought to suppress appetite^{18,19}. Advocates of such low-carbohydrate, ketogenic diets often recommend consumption of a variety of animal products and non-starchy vegetables while avoiding foods high in sugar and starch. In contrast, advocates of low-fat diets often recommend “whole food” plant-based diets that include both starchy and non-starchy vegetables in addition to grains and legumes with limited use of oils, cooking fats, and spreads.

We sought to investigate exemplars of an animal-based, ketogenic, low-carbohydrate (ABLC) diet with ~10% of energy from carbohydrates, ~75% from fat, and high energy density (~2 kcal/g) in comparison to a plant-based, low-fat (PBLF) diet with ~10% of energy from fat, ~75% from carbohydrate, and low energy density (~1 kcal/g). We conducted an inpatient crossover study in 20 adults without diabetes who were exposed to both ABLC and PBLF diets for two weeks each in random order. The first primary outcome compared the mean energy intake between each two-week diet period. The second primary outcome compared the mean energy intake on the second week of each diet period to allow for physiological adaptations to the diets and dissipation of any carryover effects.

Results

We admitted 11 male and 9 female weight-stable adults aged (mean \pm SE) 29.9 \pm 1.4 y with BMI=27.8 \pm 1.3 kg/m² as inpatients to the Metabolic Clinical Research Unit (MCRU) at the NIH Clinical Center where they resided for a continuous 28-day period (see Table 1 for baseline anthropometric and demographics). Subjects were randomly assigned to either the ABLC or PBLF diet for two weeks immediately followed by the alternate diet for the final two weeks (Figure 1). Subjects were not informed of the primary aims of the study but were told that the purpose of the study was to learn about how diets varying in carbohydrate and fat affect the body. The subjects were told that this was not a weight loss study and that they should not be trying to change their weight. They wore loose fitting clothing throughout the study and were blinded to daily weight, ketone, and continuous glucose measurements.

During each diet phase, the subjects were presented with three daily meals at standardized times and a continuous supply of snacks and bottled water. Daily food and beverages were provided at twice each subject's estimated energy requirements (calculated as 1.6 \times resting energy expenditure) and subjects were instructed to consume as much or as little as desired. Up to 60 minutes was allotted to consume each meal. Menus rotated on a 7-day schedule and the meals were designed to be well-matched across diets for total energy, protein, and non-starchy vegetables. However, the diets differed widely in energy density and the percentage of energy derived from carbohydrate versus fat such that the ABLC diet contained 10.0% of total energy from carbohydrate, 75.8% fat, 14.2% protein and had a non-beverage energy density of 2.2 kcal/g, while the PBLF diet contained 10.3% of total energy from fat, 75.2% carbohydrate, 14.5% protein, and had a non-beverage energy density of 1.1 kcal/g (Table 2). The ABLC meals derived 82% of energy from animal products whereas the PBLF meals contained only plant-based products. For details of the foods and beverages provided, please see the Supplementary Materials.

Food Intake

Figure 2A shows that the time course of daily *ad libitum* energy intake during the PBLF diet was 689 \pm 73 kcal/d lower than the ABLC diet over the two-week test periods ($p<0.0001$). There were no significant effects of diet order ($p=0.32$) or sex ($p=0.13$). During the second week of each diet period, energy intake was 544 \pm 68 kcal/d lower during the PBLF diet compared to the ABLC diet ($p<0.0001$). Whereas energy intake was not significantly different between the first and second week of the PBLF diet (14 \pm 46 kcal/d; $p=0.77$), energy intake during the second week of the ABLC diet was 312 \pm 46 kcal/d lower than the first week ($p<0.0001$).

Figure 2B plots the two-week average energy intake values for each individual subject showing that all participants consumed fewer energy during the PBLF diet compared to the ABLC diet. Similar results were found for the final week on each diet (not shown).

Figure 2C shows that the macronutrient composition of the consumed foods and beverages was similar to those presented (Table 2), with ABLC consumption being $9.9 \pm 0.3\%$ carbohydrate, $74.6 \pm 0.2\%$ fat, and $15.5 \pm 0.2\%$ protein and PBLF consumption being $10.5 \pm 0.2\%$ fat, $75.5 \pm 0.3\%$ carbohydrate, and $14.0 \pm 0.2\%$ protein. While carbohydrate and fat intake obviously differed between the diets ($p < 0.0001$), protein intake was lower during the PBLF diet, both in absolute terms (-136 ± 14 kcal/d; $p < 0.0001$) as well as when expressed as a fraction of the energy consumed ($14.0 \pm 0.2\%$ with PBLF versus $15.5 \pm 0.2\%$ with ABLC; $p < 0.0001$).

Energy intake during the PBLF diet was lower than the ABLC diet at breakfast (-241 ± 39 kcal/d; $p < 0.0001$), lunch (-143 ± 36 kcal/d; $p = 0.0008$), dinner (-195 ± 37 kcal/d; $p < 0.0001$) and snacks (-128 ± 36 kcal/d; $p = 0.002$). Energy density of the consumed foods was significantly lower with the PBLF diet as compared to the ABLC diet (0.96 ± 0.03 kcal/g with PBLF versus 1.9 ± 0.03 kcal/g with ABLC; $p < 0.0001$). A significantly greater mass of food was consumed during the PBLF diet as compared to the ABLC diet (2140 ± 43 g/d with PBLF versus 1473 ± 43 g/d with ABLC; $p < 0.0001$). Dietary fiber intake was significantly greater during the PBLF diet (60.8 ± 2.2 g/d with PBLF versus 20.5 ± 2.2 g/d with ABLC; $p < 0.0001$) whereas sodium intake was significantly greater during the ABLC diet (3725 ± 187 mg/d with PBLF versus 5938 ± 187 mg/d with ABLC; $p < 0.0001$).

Appetitive measurements and Eating Rate

Figure 2D shows that there were no significant differences in the reported pleasantness (0.21 ± 2.7 ; $p = 0.94$) or familiarity (-3.4 ± 3.0 ; $p = 0.26$) between the PBLF and ABLC meals rated on a continuous 100-point visual analogue scale. Furthermore, Figure 2E shows that subjects reported no significant differences in hunger (1.5 ± 1.4 ; $p = 0.3$), satisfaction (-1.5 ± 1.4 ; $p = 0.31$), fullness (0.74 ± 1.5 ; $p = 0.6$), or eating capacity (2.3 ± 1.6 ; $p = 0.16$) between the PBLF and ABLC diets despite large differences in energy intake.

Figure 2F shows that the PBLF meals were eaten more quickly in terms of grams per minute as compared to the ABLC meals (33.8 ± 0.90 g/min with PBLF versus 25.7 ± 0.90 g/min with ABLC; $p < 0.0001$) but the higher energy density of the ABLC meals resulted in a faster energy intake rate compared with the PBLF meals (30.9 ± 0.99 kcal/min with PBLF versus 44.2 ± 0.99 kcal/min with ABLC; $p < 0.0001$). Average meal duration was slightly longer with the PBLF diet as compared to the ABLC diet (22.9 ± 0.6 min with PBLF versus 20.8 ± 0.6 min with ABLC; $p = 0.007$).

Energy expenditure and physical activity

Table 3 shows that 24-hour energy expenditure in the respiratory chamber was 166 ± 23 kcal/d lower during the PBLF diet compared to the ABLC diet ($p < 0.0001$) which partially compensated for the reduced *ad libitum* energy intake with the PBLF diet with respect to overall energy balance. Both sedentary expenditure (-175 ± 30 kcal/d; $p < 0.0001$) and sleeping energy expenditure (-191 ± 19 kcal/d; $p < 0.0001$) were lower during the PBLF diet. Physical activity expenditure was not significantly different (-4 ± 29 kcal/d; $p = 0.88$) which corresponds to the accelerometry measurements that revealed no significant differences between the 2-week diet periods (average daily metabolic equivalents 1.503 ± 0.0017 with ABLC versus 1.502 ± 0.0017 with PBLF; $p = 0.82$).

Body weight and composition

Body weight decreased during both diets as illustrated in Figure 3A. The ABLC diet resulted in rapid weight loss during the first week and total weight loss after two weeks was 1.77 ± 0.32 kg ($p < 0.0001$). The PBLF diet led to slower initial weight loss, but after two weeks weight loss amounted to 1.09 ± 0.32 kg ($p = 0.003$) which was not significantly different from the ABLC diet ($p = 0.15$). Figure 3B indicates that most of the weight changes with the ABLC diet were due to changes in fat-free mass measured by dual-energy X-ray absorptiometry (-1.61 ± 0.27 kg; $p < 0.0001$) whereas the PBLF diet did not result in a significant change in fat-free mass (-0.16 ± 0.27 kg; $p = 0.56$). Figure 3C shows that the ABLC diet did not result in a significant change in body fat after either the first week (0.09 ± 0.12 kg; $p = 0.47$) or the second week (-0.18 ± 0.19 kg; $p = 0.34$) whereas the PBLF diet resulted in significant changes in fat mass after both the first week (-0.27 ± 0.12 kg; $p = 0.038$) and the second week (-0.67 ± 0.19 kg; $p = 0.001$). While there was no statistically significant difference in the final amount of body fat lost at the end of the PBLF and ABLC diet periods (0.48 ± 0.27 kg; $p = 0.085$), the difference in the average rate of body fat loss between the diets was 35 ± 14 g/d ($p = 0.019$) with the PBLF diet resulting in body fat loss at an average rate of 51 ± 9 g/d ($p < 0.0001$) versus 16 ± 9.7 g/d ($p = 0.11$) with the ABLC diet.

Liver fat was measured by magnetic resonance spectroscopy in 16 subjects whose baseline liver fat was $3.4 \pm 0.5\%$ and was not significantly different after either the PBLF diet ($3.4 \pm 0.5\%$; $p = 0.99$) or ABLC diet ($2.8 \pm 0.5\%$; $p = 0.36$).

Continuous Glucose Monitoring and Daily Capillary β -Hydroxybutyrate

All subjects wore continuous glucose monitors throughout the study. Figure 4A illustrates the PBLF diet resulted in greater mean glucose levels (94.3 ± 1.6 mg/dl with PBLF vs 81.3 ± 0.6 mg/dl with ABLC; $p < 0.0001$) and its coefficient of variation (18.4 ± 0.5 % with PBLF vs 13.5 ± 0.5 % with ABLC; $p < 0.0001$). Figure 4B shows that postprandial glucose was significantly higher following the PBLF meals, with mean glucose in the two

hours following the PBLF meals of 102.5 ± 0.7 mg/dl as compared to 80.5 ± 0.8 mg/dl following the ABLC meals ($p < 0.0001$).

In 15 subjects, we measured daily capillary β -hydroxybutyrate in the overnight fasted state. Figure 4C shows that the ABLC diet led to an increase in capillary β -hydroxybutyrate that quickly surpassed the 0.5 mM threshold defining a state of nutritional ketosis. During the second week of the ABLC diet, capillary β -hydroxybutyrate reached an average of 1.8 ± 0.1 mM where it remained stable (0.06 ± 0.04 mM/d; $p = 0.18$). In contrast, the PBLF diet resulted in a low concentration of capillary β -hydroxybutyrate averaging 0.2 ± 0.1 mM during the second week which was significantly lower than during the ABLC diet ($p < 0.0001$).

Meal Tests

During the second week of each diet phase, a liquid meal test was performed in the overnight fasted state. The macronutrient composition of the test meal matched the prevailing diet composition and its energy content was 30% of each participant's calculated energy requirements. Figure 5 illustrates that the low-fat meal compared to the low-carbohydrate meal led to significant increases in average postprandial glucose (101 ± 2 mg/dl with PBLF vs 88 ± 2 mg/dl with ABLC; $p < 0.0001$), insulin (47.6 ± 5.2 μ U/ml with PBLF vs 14.9 ± 5.0 μ U/ml with ABLC; $p = 0.0003$), C-peptide (4.9 ± 0.2 ng/ml with PBLF vs 2.5 ± 0.2 ng/ml with ABLC; $p < 0.0001$), and lactate (1.59 ± 0.04 mmol/L with PBLF vs 0.75 ± 0.04 mmol/L with ABLC; $p < 0.0001$). Postprandial free-fatty acids were substantially lower following the low-fat meal compared to the low-carbohydrate meal (233 ± 21 μ mol/L with PBLF vs 764 ± 20 μ mol/L with ABLC; $p < 0.0001$). Interestingly, the ABLC diet resulted in fasting triglycerides were lower compared to the PBLF diet, but the peak triglyceride concentration was much higher following the low-carbohydrate meal such that the average postprandial triglyceride was significantly higher following the low-carbohydrate meal compared to the low-fat meal (96.1 ± 7.4 mg/dl with PBLF vs 125.2 ± 7.4 mg/dl with ABLC; $p = 0.014$).

Glucose Tolerance

At the end of each diet phase, an oral glucose tolerance test (OGTT) was performed. As illustrated in Figure 6, the ABLC diet resulted in a relative impairment of glucose tolerance compared to the PBLF diet. Mean glucose during the OGTT was 115.6 ± 2.9 mg/dl with the PBLF diet as compared with 143.3 ± 2.9 mg/dl with the ABLC diet ($p < 0.0001$). Glucose measured at two hours was 108.5 ± 4.3 mg/dl with the PBLF diet as compared with 142.6 ± 4.3 mg/dl with the ABLC diet ($p < 0.0001$). The two-hour glucose measurement exceeded the ≥ 140 mg/dl threshold defining impaired glucose tolerance in 9 subjects during the ABLC diet as compared to only 3 of these same subjects during the PBLF diet.

During the OGTT, there were no significant diet differences in mean insulin (85.5 ± 6.6 $\mu\text{U}/\text{ml}$ with PBLF vs 97.8 ± 6.6 $\mu\text{U}/\text{ml}$ with ABLC; $p=0.21$) or C-peptide (8.8 ± 0.3 ng/ml with PBLF vs 9.1 ± 0.3 ng/ml with ABLC; $p=0.47$). Mean lactate was significantly higher after the PBLF diet (1.35 ± 0.05 mmol/L with PBLF vs 1.09 ± 0.05 mmol/L with ABLC; $p=0.0007$) whereas mean free-fatty acids were significantly lower following the PBLF diet (174.8 ± 21 $\mu\text{mol}/\text{L}$ with PBLF vs 346.5 ± 21 $\mu\text{mol}/\text{L}$ with ABLC; $p<0.0001$).

Blood pressure and pulse rate

Blood pressure and pulse rate were measured daily throughout the month-long inpatient stay. The PBLF diet resulted in significantly lower systolic blood pressure (112.2 ± 0.4 mmHg with PBLF versus 115.8 ± 0.4 mmHg with ABLC; $p<0.0001$), diastolic blood pressure (66.9 ± 0.4 mmHg with PBLF versus 68.5 ± 0.4 mmHg with ABLC; $p=0.0012$), and pulse rate (72.6 ± 0.5 bpm with PBLF versus 76.9 ± 0.5 bpm with ABLC; $p<0.0001$) compared to the ABLC diet.

Fasting blood measurements

Table 4 shows that both the ABLC and PBLF diets led to widespread changes in a variety of fasting blood measurements. Glucose and insulin significantly decreased compared to baseline with both ABLC and PBLF diets but were not significantly different from each other. C-peptide was significantly lower during the ABLC diet as compared to either baseline or the PBLF diet indicating a reduction in insulin secretion. Ketones were significantly increased during the ABLC diet reaching a level of ~ 3 mM compared to ~ 0.2 mM during the PBLF diet. Free fatty acids increased from baseline with both diets, but to a significantly greater degree with the ABLC diet. Triglycerides increased from baseline with the PBLF diet and tended to decrease with the ABLC diet. VLDL particle numbers decreased from baseline with the ABLC diet and increased with the PBLF diet, but there were no significant differences in VLDL particle size. Total and LDL cholesterol decreased significantly on the PBLF diet as compared to both baseline and the ABLC diet which were not significantly different from each other. LDL particle number decreased with the PBLF diet and increased with the ABLC diet. The ABLC diet led to a shift in LDL particle size distribution towards a greater number of small LDL particles. Apolipoprotein-B concentrations decreased from baseline with the PBLF diet as compared to baseline or ABLC diet which were not significantly different from each other. Both HDL cholesterol and apolipoprotein-A-1 decreased from baseline with both diets, but to a greater extent with the PBLF diet.

Except for lower TSH, the thyroid hormones were not significantly changed from baseline with the PBLF diet. In contrast, the ABLC diet resulted in significant decreases in all thyroid hormones except TSH and total T4. Branched-chain amino acids increased from baseline with the ABLC diet and decreased with the PBLF diet whereas the

gluconeogenic amino acid alanine decreased with the ABLC diet. Uric acid was significantly increased with the ABLC diet compared to both baseline and the PBLF diet. Inflammatory markers C-reactive protein and GlycA were both significantly decreased from baseline with the PBLF diet whereas only GlycA was reduced with the ABLC diet, but to a significantly greater extent than the PBLF diet.

Discussion

Our study was designed to measure *ad libitum* energy intake when inpatient subjects were exposed to widely different food environments with meals and snacks corresponding to either an exemplary plant-based, low-fat diet versus an exemplary animal-based, ketogenic, low-carbohydrate diet. The PBLF diet had a much higher glycemic load and resulted in greater postprandial glucose and insulin levels compared with the ABLC diet that was much higher in energy density. Energy intake during the PBLF diet was spontaneously reduced by ~550-700 kcal/d compared to the ABLC diet with subjects losing weight and body fat while reporting no significant differences in hunger, fullness, satisfaction, or pleasantness of the meals. These data suggest that while the ABLC diet had benefits for reducing glucose and insulin levels, the PBLF diet had benefits for appetite control.

No previous inpatient study has measured *ad libitum* food intake comparing two diets that restricted their targeted macronutrients to $\leq 10\%$ of total energy. Therefore, previous studies may not have tested diets that were sufficiently low in their targeted macronutrients to potentially reveal the benefits of one diet over another. Two metabolic ward studies found that lower fat diets (15-20% of total energy from fat) resulted in ~630-880 kcal/d less energy intake over 14 days as compared with diets higher in fat when presented to healthy volunteers in random order^{16,20}. However, the high fat diets contained 29-42% of total energy from carbohydrate which may have been too high to induce substantial decreases in insulin secretion or increases in ketones that are thought to mediate the appetite-suppressing benefits of low-carbohydrate diets^{18,19}. A non-randomized metabolic ward study of subjects with obesity and type 2 diabetes found that after 7 days of consuming a weight-maintaining “usual diet”, a very low-carbohydrate diet (~4% of energy from carbohydrates) decreased *ad libitum* energy intake by ~950 kcal/d over the next 14 days¹⁵. However, the “usual diet” was not low in fat (44% of total energy from fat) and included a variety of ultra-processed foods that may promote excess energy intake²¹. Finally, an outpatient randomized controlled feeding study of men with obesity found that a high-protein ketogenic diet (5% carbohydrates, 65% fat, 30% protein) resulted in a modest ~170 kcal/d lower *ad libitum* energy intake compared to a moderate carbohydrate diet with matched protein and energy density (36% carbohydrate, 34% fat, 30% protein)²².

A limitation of our study is that it did not include a weight-maintenance run-in period or a washout period between test diets. These design choices were made to lessen the burden on the subjects and reduce the likelihood of dropouts. To partially address the lack of run-in or washout periods, as well as allow for establishment of ketosis during the ABLC diet, we pre-specified a second primary outcome to compare *ad libitum* energy intake during the second week of each test diet period. We found that energy intake on the PBLF diet was stable over both weeks and persistently lower than the ABLC diet. Energy intake during the ABLC diet was significantly decreased during the second week as compared with the first and corresponded with the rise in capillary β -hydroxybutyrate from very low levels at the beginning of the first week of the ABLC diet and remained stable at ~2 mM during the second week. It is intriguing to speculate that the observed ~300 kcal/d reduction in energy intake from the first to second week of the ABLC diet corresponds to the magnitude of appetite suppressive effect of ketones.

Whether long-term adaptations to the ABLC diet would result in reduced appetite and energy intake compared to the PBLF diet is unknown. The physiological process of adapting to a ketogenic diet is multifaceted, involving multiple organ systems, and play out over a variety of time scales²³. Impaired glucose tolerance established at the end of the second week of the ABLC diet likely indicates a significant degree of physiological adaptation to the low-carbohydrate, high-fat diet rather than a pathophysiological response. Daily respiratory quotient was ~0.75 during the ABLC diet indicating a substantial increase in fat and ketone oxidation which has previously been shown to occur within the first week of adaptation to a ketogenic diet with no further decreases over the next several weeks²⁴. Nutritional ketosis was established within several days of instituting the ABLC diet and capillary β -hydroxybutyrate was stable during the second week of the diet. An isocaloric ketogenic diet has been shown to result in stable fasting blood ketones at weeks two, three, and four of an inpatient metabolic ward study²⁴ suggesting that we would not necessarily expect further increases in total blood ketones beyond ~3 mM at the end of the second week of the ABLC diet. Therefore, several metrics suggest a substantial degree of physiological adaptation to the ABLC diet had already occurred by two weeks. However, circulating uric acid remained ~35% elevated at the end of the second week of the ABLC diet which may indicate that keto-adaptation was not yet complete. It remains to be determined whether prolonged exposure to the ABLC diet would result in an additional reduction in energy intake needed to match the level of the PBLF diet.

Despite the substantial differences in energy intake between the PBLF and ABLC diets, total weight loss after two weeks was surprisingly similar. Greater weight loss during the first week of the ABLC diet as compared to the PBLF diet was likely due to differences in body water, glycogen, and gastrointestinal contents. Indeed, fat-free mass was decreased significantly with the ABLC diet whereas fat-free mass was preserved with the PBLF diet. While the ABLC diet did not induce significant body fat loss, it resulted in greater early weight loss despite higher energy intake than the PBLF diet.

Unlike the PBLF diet that resulted in significant loss of body fat, the ABLC diet had no significant body fat changes suggesting that energy intake during the ABLC diet was

approximately equivalent to the total amount of energy that was expended. The rate of body fat loss during the PBLF diet was ~35 g/d greater as compared to the ABLC diet which corresponds to a difference in energy balance of ~330 kcal/d between the diets which was somewhat smaller than the observed differences in energy intake between the PBLF and ABLC diets. Indeed, energy expenditure as measured in the respiratory chambers was ~150-200 kcal/d lower during the PBLF diet as compared to the ABLC diet and therefore partially compensated for the reduced energy intake during the PBLF diet.

In accordance with previous studies ^{24,25}, the approximately eucaloric ABLC diet with ~15% protein likely led to very little changes in energy expenditure compared to baseline. In contrast, the ~700 kcal/d decrease in energy intake during the PBLF diet likely resulted in decreased energy expenditure. While we previously observed that a controlled ~800 kcal/d selective reduction of dietary fat from an energy balanced baseline diet led to a nonsignificant ~50 kcal/d decrease in 24-hour energy expenditure ²⁶, the diet used in the previous study was composed of ~8% fat, 71% carbohydrate, and 21% protein and was therefore significantly higher in protein compared to the ~14% protein content of the PBLF diet. Because dietary protein is more thermogenic than carbohydrate or fat ²⁷, the comparatively higher protein intake in our previous study may have been responsible for the relative maintenance of 24-hour energy expenditure as compared to the PBLF diet in the present study that resulted in a ~150-200 kcal/d decrease in expenditure.

Both the ABLC and PBLF diets led to favorable changes fasting glucose, insulin, and markers of inflammation compared to baseline. Blood pressure and pulse rate were lower during the PBLF diet as compared to the ABLC diet. The PBLF diet led to a significant decrease in branched-chain amino acids which are thought to play a role in metabolic disease ²⁸ whereas the ABLC diet led to significant increases in branched-chain amino acids compared to both baseline and the PBLF diet. Both diets led to decreases in HDL cholesterol and apolipoprotein-A-1 compared to baseline, but these parameters were decreased to a greater degree with the PBLF diet. However, the PBLF diet resulted in decreased total cholesterol, LDL cholesterol, and apolipoprotein-B concentrations, whereas these parameters were unchanged from baseline in the ABLC diet. Surprisingly, the ABLC diet appeared to shift the LDL particle size distribution towards smaller particles as compared to baseline which is the opposite of what is expected for low-carbohydrate diets ^{29,30}. Our study cannot distinguish whether differences in fasting blood levels between the PBLF and ABLC diets were primarily attributable to composition differences between the diets or the substantial differences in *ad libitum* energy intake and overall energy balance.

Both fasting and postprandial triglycerides are thought to increase risk for cardiovascular disease ³¹. The ABLC diet resulted in decreased fasting triglycerides compared to baseline whereas the PBLF diet increased fasting triglycerides. Interestingly, despite lower fasting triglycerides during the ABLC diet, postprandial triglycerides were higher following the low-carbohydrate test meal compared to the isocaloric low-fat test meal likely due to the very high fat content of the low-carbohydrate

meal. In contrast, the low-fat meal led to higher postprandial glucose and insulin levels. The CGM measurements of interstitial glucose concentrations demonstrated that both mean and postprandial glucose excursions were much larger throughout the PBLF diet period as compared to the ABLC diet. This is of potential concern because high glucose variability is thought to be a risk factor for coronary artery disease ³². Interestingly, postprandial lactate concentrations were much higher following the PBLF meal as compared to the ABLC meal, likely due to increased glucose uptake and glycolysis after the PBLF meal. High lactate levels may have widespread implications for immune modulation as well as oncogenesis ³³.

What was the mechanism for the reduced *ad libitum* energy intake in the PBLF diet as compared to the ABLC diet? Despite the similar protein content of the ABLC and PBLF diets that were presented to the subjects, protein intake during the ABLC diet was increased as compared to the PBLF diet. However, in contrast to the observed differences in energy intake, the higher protein consumed in the ABLC diet would be expected to increase satiety and decrease energy intake as compared with the PBLF diet ^{27,34}. However, the greater dietary fiber and significantly lower non-beverage energy density of the PBLF diet likely promoted a reduction in energy intake as compared to the ABLC diet ³⁵⁻³⁸. Indeed, the ABLC diet was at the 75th percentile for US population non-beverage energy density whereas the PBLF diet was below the 25th percentile ³⁹.

However, the determinants of *ad libitum* energy intake and overall energy balance are likely quite complex as suggested by comparison with our previous study of *ad libitum* energy intake with ultra-processed versus unprocessed diets ²¹. The ultra-processed and unprocessed diets had non-beverage energy densities that closely matched the ABLC and PBLF diets of the present study, respectively. The PBLF diet and the unprocessed diet both contained high amounts of fiber. However, more body fat was lost with the PBLF diet as compared to the unprocessed diet indicating a greater degree of negative energy balance despite the higher glycemic load of the PBLF diet. Interestingly, while the ABLC diet had a similar non-beverage energy density to the ultra-processed diet and was lower in dietary fiber, only the ultra-processed diet led to gain of weight and body fat. While such cross-study comparisons are obviously imperfect, they suggest that the determinants of energy intake and body fat change cannot be adequately explained by individual factors like glycemic load, protein intake, energy-density, and dietary fiber.

The main limitation of our study is that the inpatient environment makes it difficult to generalize our results to the real world. Indeed, it is important to emphasize that our study did not examine the effects of diet recommendations for weight loss which often involve targeted reductions of carbohydrate or fat along with instructions regarding the types of foods allowed or to be avoided. Due to the controlled food environment in our study, the only choice available to our subjects was how much of the presented foods and beverages to consume. The subjects were told that this was not a weight loss study, were instructed not to attempt to change their weight, and were blinded to their body weight measurements. Whether our results would have been different in subjects actively trying to lose weight is unknown.

Conclusion

The passive overconsumption model of obesity predicts that consuming a diet with high energy density results in excess energy intake and weight gain. The carbohydrate-insulin model of obesity predicts that consuming a diet with high glycemic carbohydrates results in increased postprandial insulin that drives body fat accumulation thereby increasing hunger and energy intake. While our PBLF diet contained foods with high glycemic load that significantly increased postprandial glucose and insulin levels compared to the ABLC diet, the PBLF diet led to less energy intake compared with the ABLC diet which contradicts the predictions of the carbohydrate-insulin model. While the ABLC diet was high in energy density, it did not result in net body fat gain which challenges the validity of the passive over consumption model. Our results suggest that regulation of energy intake and body weight are more complex than these and other simple models propose.

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Declaration of Interests

CG Forde has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, serves on the scientific advisory council for Kerry Taste and Nutrition, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. The other authors have no conflicts of interest.

Figure Legends

Figure 1. Overview of the study design. Twenty adults were confined to metabolic wards where they were randomized to consume either an animal-based, low-carbohydrate, ketogenic diet or a plant-based, low-fat diet for 2 consecutive weeks followed immediately by the alternate diet. Body weight, vital signs, and capillary β -hydroxybutyrate were measured daily in the overnight fasted state. Accelerometers and continuous glucose monitors were worn throughout. Every week, subjects spent one day residing in a respiratory chamber to measure energy expenditure. Body composition was measured by dual-energy X-ray absorptiometry (DXA) and liver fat was measured by magnetic resonance imaging/spectroscopy (MRI/MRS) as indicated. Meal tests and oral glucose tolerance tests were performed towards the end of the second week on each diet.

Figure 2. Ad libitum food intake, appetite and eating rate. A) Energy intake was lower during the two-week plant-based, low-fat (PBLF) diet as compared to the animal-based, ketogenic low-carbohydrate (ABLC) diet. B) Individual subject responses show that all subjects consumed less energy during the PBLF diet. C) Average macronutrient intake during the two-week diet periods revealed that consumption of the ABLC and PBLF diets generally matched the presented macronutrient distributions, but the ABLC diet resulted in significant increases in protein intake. D) Both diets were rated similarly on visual analogue scales (VAS) with respect to pleasantness and familiarity. E) Appetitive measures were not significantly different between the diets. F) Meal eating rate was significantly greater during the ABLC diet in terms of kcals per minute but lower in terms of grams per minute as compared to the PBLF diet.

Figure 3. Body weight and composition changes. A) Both the ABLC and PBLF diets led to progressive weight loss over time with the ABLC diet resulting in more rapid weight loss during the first week. B) Fat-free mass decreased significantly only during the ABLC and accounted for the majority of the observed weight loss. C) Body fat mass decreased with the PBLF diet but was not significantly decreased with the ABLC diet.

Figure 4. Continuous Glucose Monitoring and Daily Capillary β -Hydroxybutyrate. A) During the two weeks of the ABLC diet, mean glucose and its coefficient of variation measured using continuous glucose monitors were significantly lower than during the PBLF diet. B) Postprandial glucose was substantially higher following the *ad libitum* PBLF meals as compared to ABLC meals. C) The ABLC diet led to a rapid increase in fasting capillary β -hydroxybutyrate reaching a stable level during the second week. The PBLF diet resulted in a low concentration of capillary β -hydroxybutyrate throughout the study.

Figure 5. Low-fat and Low-carbohydrate Meal Tests. Mean postprandial A) glucose, B) insulin, C) C-peptide, and D) lactate were much higher following the low-fat meal test whereas E) free fatty acids, and F) triglycerides were higher following the isocaloric low-carbohydrate meal test.

Figure 6. Glucose tolerance. During a 75g oral glucose tolerance test, A) mean glucose was significantly higher at the end of the ABLC diet, whereas B) insulin was not different between the diets. C) Lactate was higher in response to the glucose tolerance test given at the end of the PBLF diet, whereas D) free fatty acids were lower.

	All (N=20)	Female (N=9)	Male (N=11)
Age (years)	29.9±1.4 (18, 39)	30.2±1.9 (19, 36)	29.5±2.2 (18, 39)
Height (m)	1.71±0.02 (1.57, 1.88)	1.63±0.02 (1.57, 1.68)	1.77±0.02 (1.66, 1.88)
Body Weight (kg)	80.8±4.1 (57.9, 126.2)	75.3±5.8 (57.9, 115.8)	85.2±5.6 (59.7, 126.2)
Body Mass Index (kg/m ²)	27.8±1.3 (20.6, 40.8)	28.2±2.0 (20.8, 40.8)	27.3±1.8 (20.6, 39.0)
Fat Mass (kg)	26.9±2.5 (7.2, 57.5)	31.4±3.7 (19.0, 57.5)	23.3±3.1 (7.2, 41.7)
Body Fat (%)	32.8±2.1 (12.0, 49.7)	40.9±1.7 (32.2, 49.7)	26.2±2.2 (12.0, 35.9)
Resting Energy Expenditure (kcal/d)	1550±64 (998, 2124)	1347±93 (998, 1973)	1717±49 (1504, 2124)

Table 1. Baseline anthropometrics of the study subjects. Mean ± SE (min, max).

	ABLC Diet	PBLF Diet
Three Daily Meals		
Energy (kcal/d)	3875	3869
Carbohydrate (%)	9.9	75.2
Fat (%)	74.4	10.6
Protein (%)	15.7	14.2
Energy Density (kcal/g)	1.72	0.92
Non-beverage Energy Density (kcal/d)	1.80	0.92
Sodium (mg/1000 kcal)	2362	2013
Fiber (g/1000 kcal)	6.8	29.9
Sugars (g/1000 kcal)	10.1	50.9
Saturated Fat (g/1000 kcal)	29.7	1.9
Monounsaturated Fat (g/1000 kcal)	25.9	2.7
Polyunsaturated Fat (g/1000 kcal)	18.7	4.2
Omega-3 Fatty Acids (g/1000 kcal)	2.2	0.5
Omega-6 Fatty Acids (g/1000 kcal)	16.5	3.1
Glycemic Index	43.4	54.8
Glycemic Load (g/1000 kcal)	30.9	347.4
Animal Products (% of energy)	82	0
Ultra-Processed Foods (% of energy)	43	34
Non-starchy vegetables (g)	1000	953
Snacks (available all day)		
Energy (kcal/d)	1291	1288
Carbohydrate (%)	10.3	75.0
Fat (%)	80.2	9.4
Protein (%)	9.5	15.6
Energy Density (kcal/g)	6.39	3.04
Sodium (mg/1000 kcal)	589	219
Fiber (g/1000 kcal)	13.8	35.9
Sugars (g/1000 kcal)	6.4	145.6
Saturated Fat (g/1000 kcal)	10.2	2.7
Monounsaturated Fat (g/1000 kcal)	51.5	2.4
Polyunsaturated Fat (g/1000 kcal)	29.3	5.8
Omega-3 Fatty Acids (g/1000 kcal)	0.8	0.7
Omega-6 Fatty Acids (g/1000 kcal)	28.5	5.1
Glycemic Index	14.2	42.3
Glycemic Load (g/1000 kcal)	2.5	90.0
Animal Products (% of energy)	0	0
Ultra-Processed Foods (% of energy)	0	0
Non-Starchy Vegetables (g)	0	0

Daily Meals + Snacks		
Energy (kcal/d)	5166	5157
Carbohydrate (%)	10.0	75.2
Fat (%)	75.8	10.3
Protein (%)	14.2	14.5
Energy Density (kcal/g)	2.1	1.11
Non-beverage Energy Density (kcal/g)	2.20	1.11
Sodium (mg/1000 kcal)	1919	1565
Fiber (g/1000 kcal)	8.5	31.4
Sugars (g/1000 kcal)	9.2	74.6
Saturated Fat (g/1000 kcal)	24.8	2.1
Monounsaturated Fat (g/1000 kcal)	32.3	2.6
Polyunsaturated Fat (g/1000 kcal)	21.4	4.6
Omega-3 Fatty Acids (g/1000 kcal)	1.82	0.51
Omega-6 Fatty Acids (g/1000 kcal)	19.5	3.6
Glycemic Index	37.5	51.7
Glycemic Load (g/1000 kcal)	33.4	437.4
Animal Products (% of energy)	61	0
Ultra-Processed Foods (% of energy)	32	26
Non-Starchy Vegetables (g)	1000	953

Table 2. Diet composition of the average 7-day rotating menu presented to the subjects during the animal-based, ketogenic, low-carbohydrate (ABLC) diet and plant-based, low-fat (PBLF) diet.

	ABLC Diet	PBLF Diet	P-value
24hr Energy Expenditure (kcal/d)	2315±16	2149±17	<0.0001
24hr Respiratory Quotient	0.753±0.005	0.885±0.005	<0.0001
Sleeping Energy Expenditure (kcal/d)	1597±13	1406±13	<0.0001
Sedentary Energy Expenditure (kcal/d)	1918±21	1743±21	<0.0001
Physical Activity Expenditure (kcal/d)	394±21	390±21	0.88

Table 3. Respiratory chamber measurements during the animal-based, ketogenic, low-carbohydrate (ABLC) and plant-based, low-fat (PBLF) diet periods. Least squares mean ± SE. Reported p-values are not adjusted for multiple comparisons.

	Baseline	ABLC Diet	P-value ABLC Diet vs. Baseline	PBLF Diet	P-value PBLF Diet vs. Baseline	P-value ABLC vs. PBLF Diet
Hgb A1C (%)	5.2±0.2	5.0±0.2	<0.0001	5.1±0.2	0.001	0.28
Glucose (mg/dl)	91.4±1.4	84.1±1.4	0.0007	85.4±1.4	0.004	0.55
Insulin (μU/ml)	11.3±0.5	7.4±0.5	<0.0001	8.3±0.5	0.0002	0.22
C-Peptide (ng/ml)	2.18±0.06	1.57±0.06	<0.0001	1.93±0.06	0.003	<0.0001
Acetoacetate (mM)	0.035±0.04	0.431±0.04	<0.0001	0.054±0.04	0.73	<0.0001
Acetone (mM)	0.023±0.07	0.567±0.07	<0.0001	0.029±0.07	0.95	<0.0001
β-hydroxybutyrate (mM)	0.089±0.2	2.01±0.2	<0.0001	0.125±0.2	0.91	<0.0001
Ketones (mM)	0.147±0.3	3.01±0.3	<0.0001	0.209±0.3	0.89	<0.0001
Free Fatty Acids (μmol/L)	328±48	760±48	<0.0001	508±48	0.01	0.0006
Triglycerides (mg/dl)	75.5±4.5	63.4±4.5	0.066	93.3±4.5	0.008	<0.0001
VLDL Particle Number (nmol/L)	39.8±3.5	18.9±3.8	0.0003	46.8±3.7	0.18	<0.0001
VLDL Size (nm)	44.1±1.4	45.6±1.8	0.53	47.2±1.6	0.16	0.50
Total Cholesterol (mg/dl)	162.5±3.9	161.2±3.9	0.8	120.7±3.9	<0.0001	<0.0001
Calc LDL Cholesterol (mg/dl)	93.2±4.0	101.6±4.0	0.14	64.5±4.0	<0.0001	<0.0001
LDL Cholesterol (mg/dl)	87.9±3.4	92.4±3.6	0.38	64.7±3.7	<0.0001	<0.0001
LDL Particle Number (nmol/L)	1072±53	1224±53	0.055	781±53	0.0006	<0.0001
LDL Particle Size (nm)	20.9±0.09	20.5±0.09	0.002	20.6±0.09	0.023	0.38
Large LDL (nmol/L)	162±19	55±20	0.0004	147±21	0.60	0.0024
Medium LDL (nmol/L)	328±46	334±47	0.93	158±50	0.016	0.013
Small LDL (nmol/L)	855±68	1130±71	0.008	692±74	0.11	0.0001
HDL Cholesterol (mg/dl)	54.4±1.3	47.1±1.3	0.0002	37.5±1.3	<0.0001	<0.0001
HDL Particle Number (nmol/L)	32.9±0.6	27.9±0.6	<0.0001	24.4±0.6	<0.0001	0.0003
HDL Size (nm)	9.31±0.06	9.28±0.06	0.67	9.28±0.06	0.72	0.95
Large HDL (nmol/L)	2.6±0.2	2.5±0.2	0.50	1.5±0.2	<0.0001	0.0002
Medium HDL (nmol/L)	4.1±0.2	2.2±0.3	<0.0001	3.0±0.3	0.002	0.05
Small HDL (nmol/L)	13.5±0.5	14.0±0.5	0.44	10.2±0.5	<0.0001	<0.0001
Apolipoprotein-A-1 (mg/dl)	130.5±2.4	117.5±2.5	0.0005	94.5±2.6	<0.0001	<0.0001

Apolipoprotein-B (mg/dl)	73.5±2.8	77.1±3.0	0.39	57.5±3.1	0.0005	<0.0001
BCAA (μmol/L)	456±17	635±17	<0.0001	353±18	0.0002	<0.0001
Valine (μmol/L)	233±8	332±8	<0.0001	176±9	<0.0001	<0.0001
Leucine (μmol/L)	162±7	201±7	0.0002	125±7	0.0006	<0.0001
Isoleucine (μmol/L)	61±4	102±4	<0.0001	52±4	0.094	<0.0001
Alanine (μmol/L)	325±12	194±13	<0.0001	310±13	0.38	<0.0001
Uric Acid (mg/dl)	5.3±0.2	7.2±0.2	<0.0001	4.8±0.2	0.17	<0.0001
TSH (μIU/ml)	2.26±0.12	2.34±0.12	0.64	1.86±0.12	0.03	0.009
Free T3 (pg/ml)	3.30±0.07	2.61±0.07	<0.0001	3.13±0.07	0.08	<0.0001
Free T4 (ng/dl)	1.26±0.02	1.35±0.02	0.002	1.27±0.02	0.73	0.006
T3 (ng/dl)	119.9±2.8	88.3±2.8	<0.0001	113.6±2.8	0.12	<0.0001
T4 (μg/dl)	7.23±0.13	6.93±0.13	0.11	6.96±0.13	0.15	0.89
hsCRP (mg/L)	2.1±0.2	2.1±0.2	0.82	1.2±0.2	0.008	0.003
GlycA (μmol/L)	349±5.7	301±6.0	<0.0001	331±6.2	0.038	0.0014

Table 4. Fasting blood measurements at baseline and at the end of the animal-based, ketogenic, low-carbohydrate (ABLC) and plant-based, low-fat (PBLF) diet periods. Least squares mean ± SE. Reported p-values are not adjusted for multiple comparisons.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes & Digestive & Kidney Diseases (NCT03407053). Eligible subjects were between 18-50 years old with a body mass index (BMI) $\geq 20\text{kg}/\text{m}^2$ and were weight-stable ($< \pm 5\%$ over the past 6 months). Volunteers were excluded if they had anemia, diabetes, cancer, thyroid disease, eating disorders or other psychiatric conditions such as clinical depression or bipolar disorder. Volunteers with strict dietary concerns, including food allergies or adherence to particular diets (e.g., vegetarian, vegan, kosher, etc.) were also excluded. One subject who was enrolled in the study was removed during their first week due to a hypoglycemia episode during the ABLC diet. All other subjects who enrolled in the study completed the four-week inpatient stay.

METHOD DETAILS

Diets

The diets were designed and analyzed using ProNutra software (version 3.4, Viocare, Inc., Princeton, NJ) with nutrient values derived from the USDA National Nutrient Database for Standard Reference, Release 26 and the USDA Food and Nutrient Database for Dietary Studies, 4.0. The meals were provided on 7-day rotating menus (see the Supplemental Information for detailed menu information). Foods and beverages were categorized according to the NOVA system⁴⁰ and glycemic index was calculated relative to 50g of oral glucose⁴¹.

Bottled water and snacks representative of the prevailing diet were provided *ad libitum* throughout the day in snack boxes located in the subjects' inpatient rooms. Meals were presented to the subjects plated approximately as shown in the photographs included in the Supplemental Information with instructions to eat as much or as little as desired. Subjects were given up to 60 minutes to eat their meals. When meals were finished, the meal duration was documented. Remaining food and beverages were identified and weighed by nutrition staff to calculate the amount of each food consumed and the nutrient and energy intake were calculated using the nutrition software described above. Meal eating rate was calculated by dividing the measured food intake by the meal duration.

Subjective assessment of appetite, sensory, and palatability:

During the second week of each diet period, subjects were asked to complete appetitive surveys over the course of three separate days implemented using REDCap (Research Electronic Data Capture) electronic data capture tools⁴². The surveys comprised visual analog scales (VAS) in response to four questions: 1) "How hungry do you feel right now?" 2) "How full do you feel right now?" 3) "How much do you want to eat right now?"

and 4) "How much do you think you can eat right now?". Subjects answered the questions using 100-point VAS line scale anchored at 0 and 100 by descriptors such as "not at all" and "extremely". The questions were answered immediately prior to each meal and at least every 30 to 60 minutes over the 2-3 hours following the consumption of each meal. We calculated the mean values of the responses adjusted for the energy consumed using multiple linear regression.

On the last two days of the first diet period and the first two days of the second diet period, subjects were asked to complete another survey to assess the palatability and familiarity of the meals provided. The questions were embedded amongst distracter "mood" ratings (e.g., alert, happy, and clear-headed). Survey items were completed after the first bite of the meal.

Body weight and composition

Daily body weight measurements were performed at 6am each morning after the first void (Welch Allyn Scale-Tronix 5702; Skaneateles Falls, NY, USA). Subjects wore hospital-issued top and bottom pajamas which were pre-weighed and deducted from scale weight. Body composition measurements were performed at baseline and weekly using dual-energy X-ray absorptiometry (General Electric Lunar iDXA; Milwaukee, WI, USA). The resulting percent body fat measurements were applied to the scale measurements on the day of the scan to calculate fat mass and fat-free mass. Because the scan days were not always conducted precisely on days 1, 7, and 14 of each diet period, the sum of the body fat and fat-free masses at the beginning, middle, and end of the diet periods do not precisely match the scale weights on days 1, 7, and 14 of the diets. The rate of body fat change during each 14-day diet period were calculated by linear regression. Liver fat measurements were performed using T1 and T2 corrected proton magnetic resonance spectroscopy with a breath-holding technique in a 3T scanner (MAGNETOM Verio; Siemens, Tarrytown, NY)⁴³.

Physical Activity Monitoring

Overall physical activity was quantified by calculating average daily metabolic equivalents (MET) using small, portable, pager-type accelerometers (Actigraph, Pensacola, FL) sampled at 80 Hz and worn on the hip⁴⁴.

Energy expenditure via respiratory chamber

All chamber measurement periods were >23 hours and we extrapolated the data to represent 24hr periods by assuming that the mean of the measured periods was representative of the 24hr period. Energy expenditure was calculated as follows:

$$EE_{chamber} (\text{kcal}) = 3.85 \times VO_2 (\text{L}) + 1.075 \times VCO_2 (\text{L})$$

where VO_2 and VCO_2 were the volumes of oxygen consumed and carbon dioxide produced, respectively.

Sleeping energy expenditure was determined by the lowest energy expenditure over a continuous 180 minute period between the hours of 00:00-06:00⁴⁵. Sedentary energy expenditure includes the thermic effect of food as previously described²⁴ and physical activity expenditure was the difference between 24-hour energy expenditure and sedentary energy expenditure.

Continuous glucose monitoring

Subjects wore the Dexcom G4 Platinum (Dexcom Inc, San Diego, CA, USA) continuous glucose monitor (CGM) daily during the inpatient stay. The device consisted of a small sensor, a transmitter, and a hand-held receiver. The sensor was inserted subcutaneously in the lower abdomen to measure interstitial glucose concentrations every 5 minutes which were transmitted to the receiver. Finger stick calibrations were required at insertion as well as each morning and night. The sensor was changed every 7 days. Subjects were blinded to their glucose readings. The CGM was removed during MRI/MRS procedures and DXA scans. All the data was downloaded at the end of the inpatient stay. Postprandial CGM data analysis was limited to 368 ABLC diet meals and 394 PBLF meals with CGM measurements of at least 105 minutes after the meal with a minimum of 20 data points.

Capillary β -Hydroxybutyrate

Capillary β -Hydroxybutyrate was measured in the overnight fasted state using the Abbott Precision Xtra blood glucose and ketone monitoring system (Abbott Diabetes Care Inc., Alameda, CA) in daily finger prick blood samples obtained from 15 subjects.

QUANTIFICATION AND STATISTICAL ANALYSIS

This study was powered to detect a difference in mean *ad libitum* energy intake of 125-150 kcal/d over 14-day test diet period and 175-210 kcal/d over the final 7 days of each diet period in 20 subjects with probability (power) of 0.8 with a Type I error probability of

0.05. This sample size calculation was informed by previous studies measuring day to day variability of *ad libitum* energy intake having a standard deviation of about 500-600 kcal/d⁴⁶⁻⁴⁸. Using the conservative assumption that within-subject energy intake correlations were zero, over a 14-day diet period each subject will have a mean energy intake with a standard error of about 130-160 kcal/d and the mean energy intake difference between the study diets will have a standard error of about 190-230 kcal/d. Over the final 7-day diet period, each subject will have a mean energy intake with a standard error of about 190-230 kcal/d and the mean energy intake difference between the study diets will have a standard error of about 270-320 kcal/d.

Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA). The baseline data and figures are presented as mean \pm SE. Data were analyzed by analysis of variance (PROC GLM, SAS). The data tables present least squares mean \pm SE and two-sided t-tests were used to compare the diet groups. Because the non-primary measurements in this study were exploratory in nature, the reported p-values were not adjusted for multiple comparisons and therefore any apparent significance of these results should be confirmed in future experiments.

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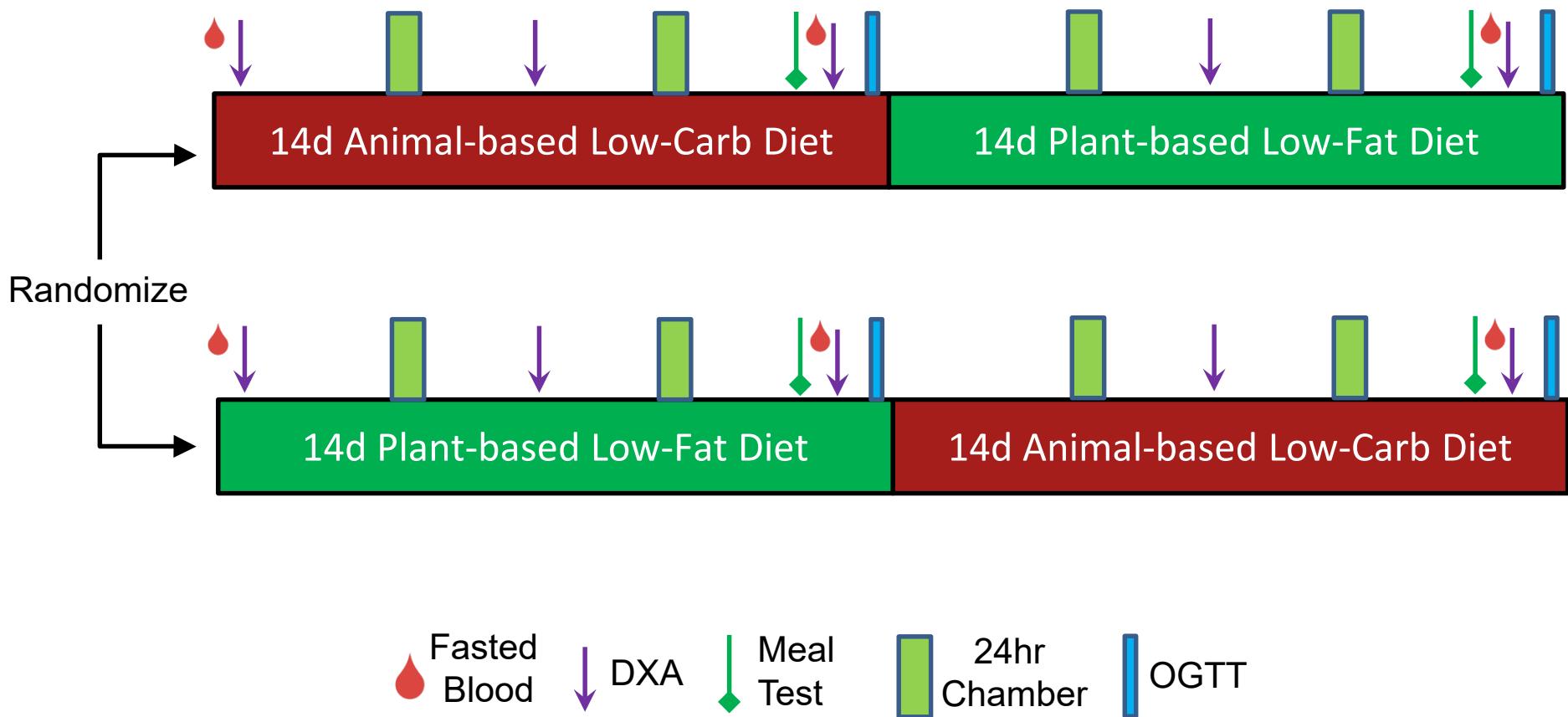


Figure 1

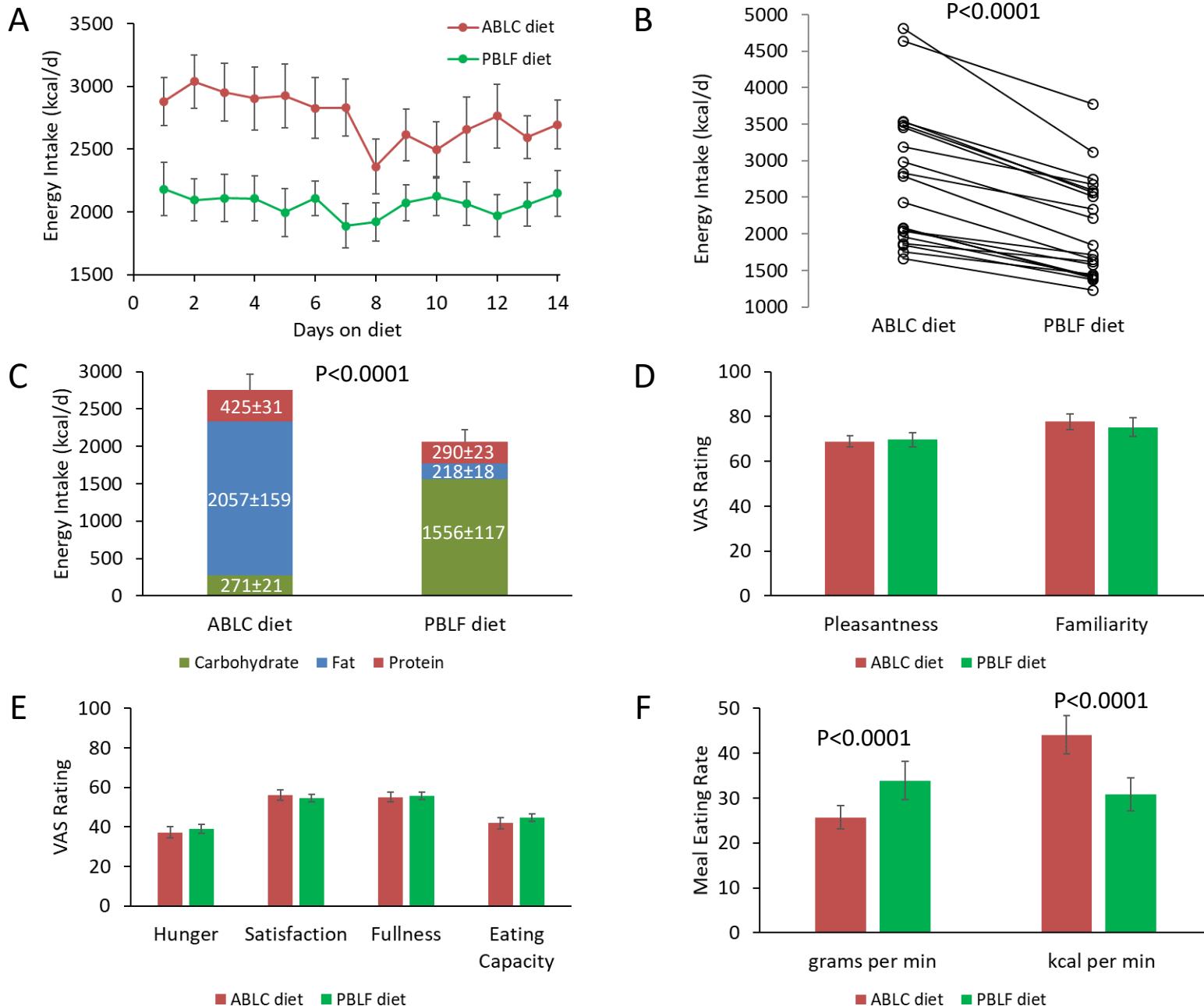


Figure 2

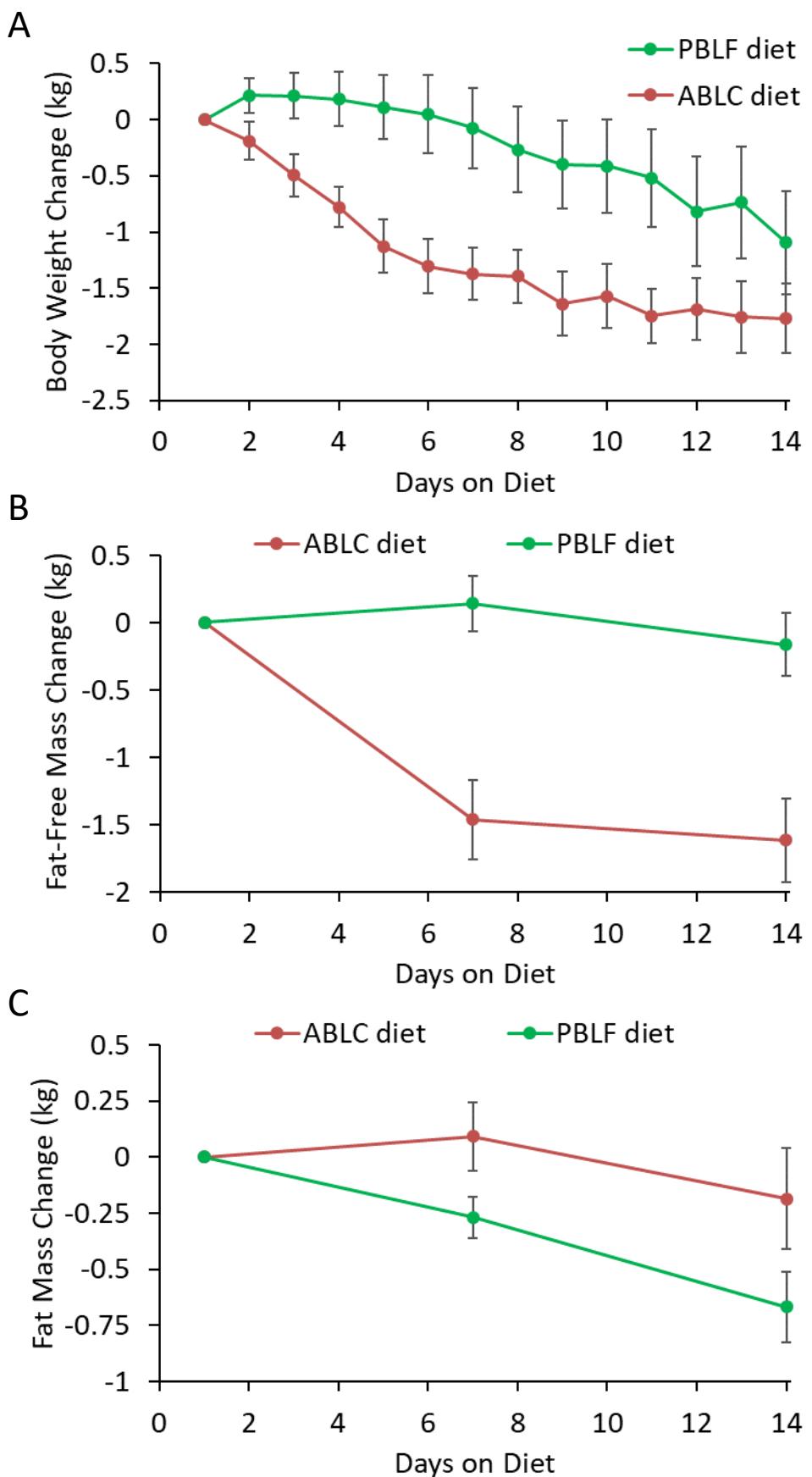


Figure 3

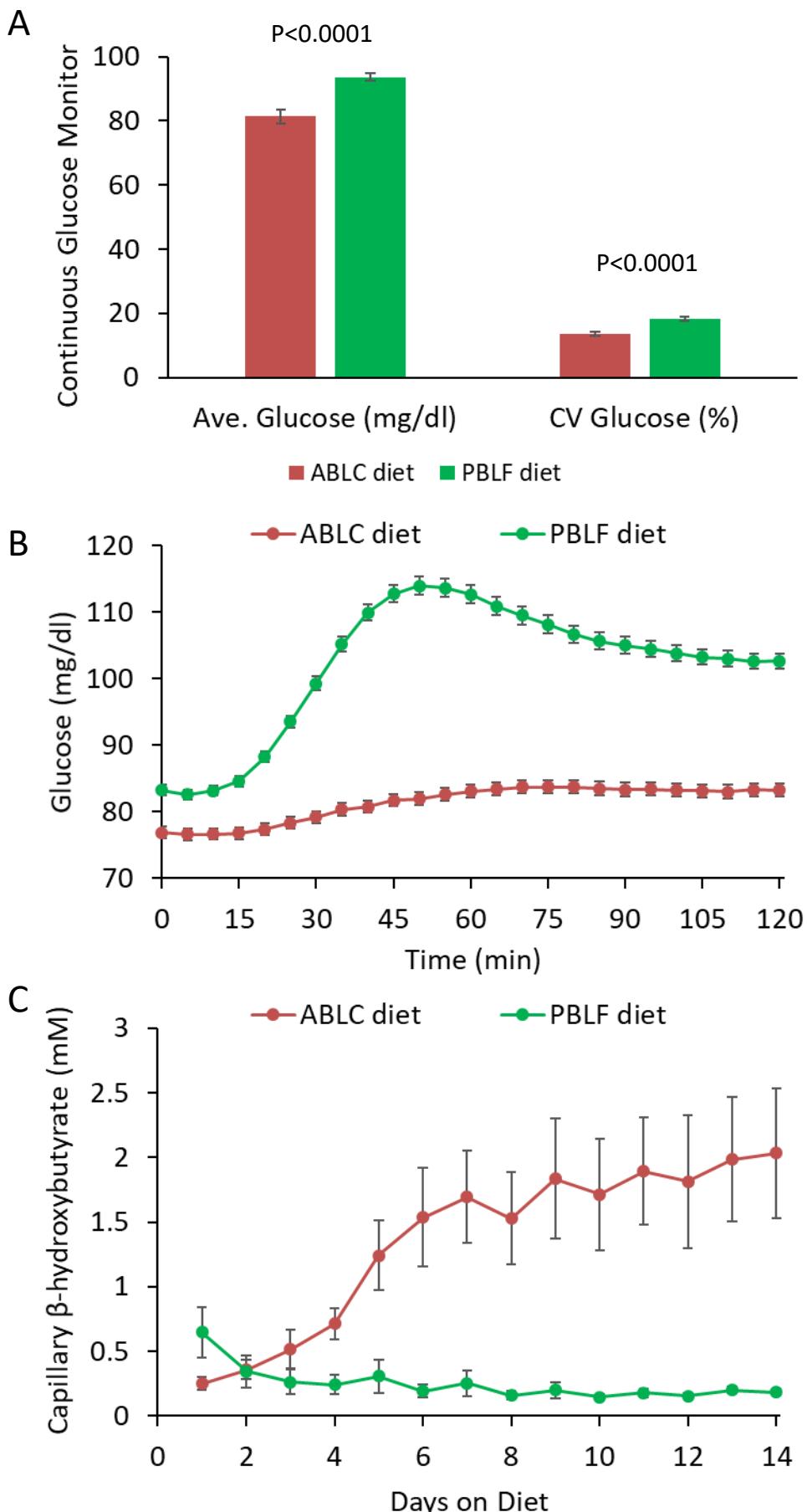


Figure 4

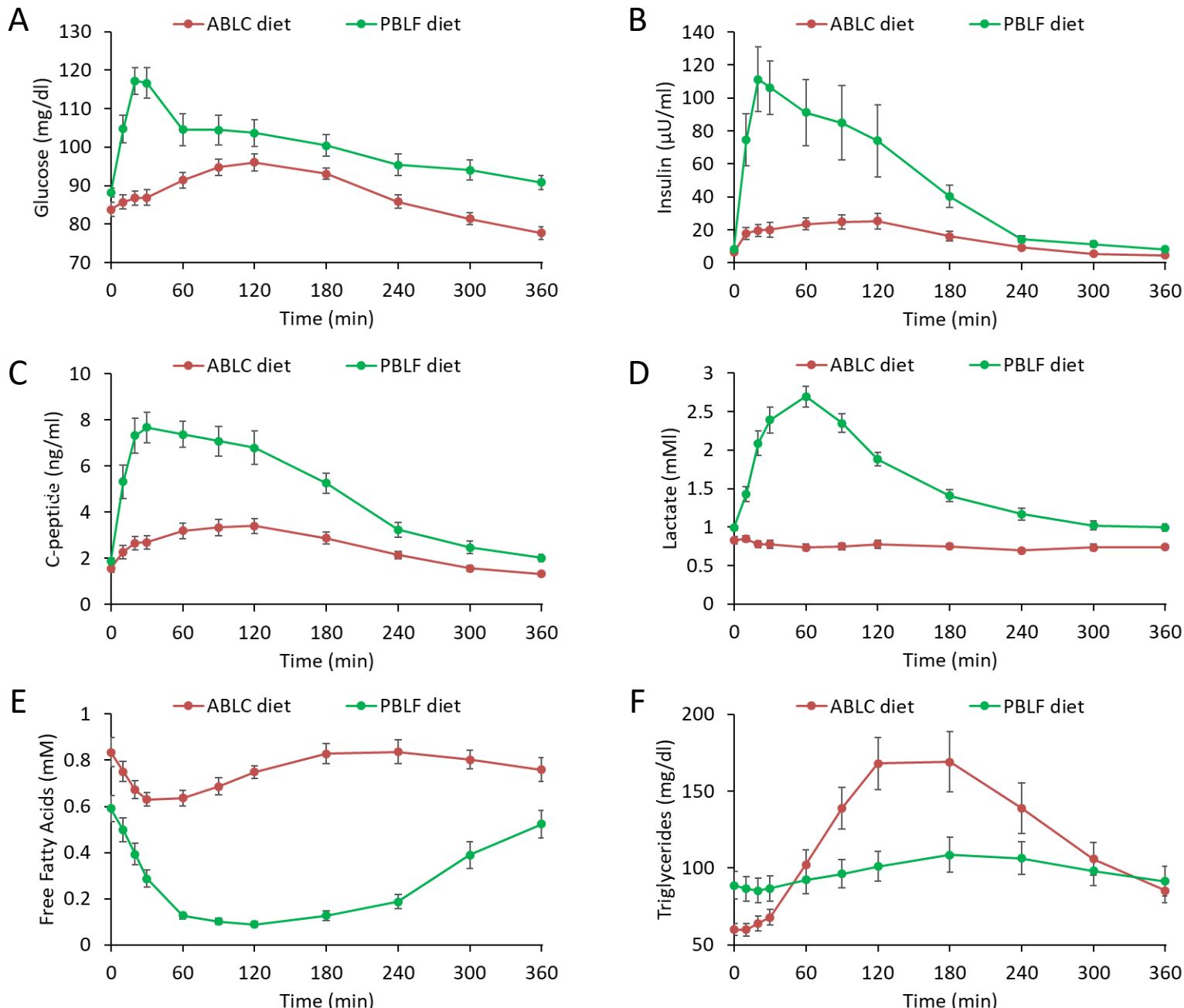


Figure 5

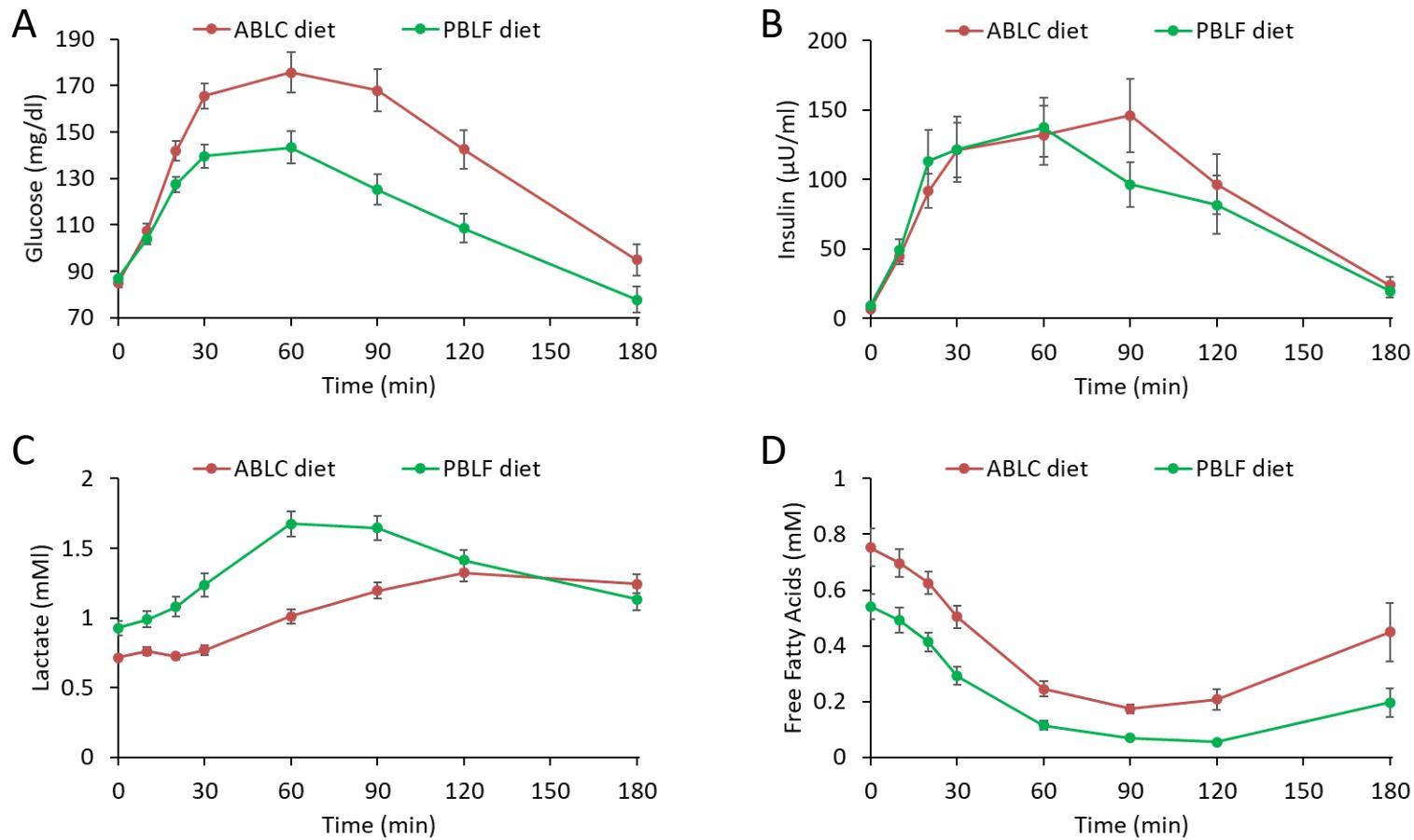


Figure 6

Supplemental Information

Animal-based, Ketogenic, Low-Carbohydrate Diet Menu

Menu 1 – 3800 kcal

Breakfast

Veggie Scramble (Egg, shredded cheddar/Monterey jack cheese, heavy cream, butter, onions, broccoli, spinach, salt)



Lunch

Burrito bowl with beef roast (green leaf lettuce, tomatoes, shredded cheddar/Monterey jack cheese, flaxseeds, and salt) with guacamole, ranch dressing, and sour cream



Dinner

Zucchini pasta with meat sauce (zucchini spirals, crushed tomatoes, butter, salt and ground beef) with parmesan cheese and a side salad (green leaf lettuce, tomatoes and cucumber) and creamy Caesar dressing



Menu 2

Breakfast

Cheesy scrambled eggs (egg, heavy cream, butter, salt, American cheese) and pork sausage.



Lunch

Tuna salad (Solid white tuna, mayonnaise, celery, salt, onions) on a bed of lettuce 2% milk and macadamia nuts



Dinner

Cauliflower, chicken and cheese soup (cauliflower, heavy cream, butter, American cheese, chicken breast, salt and pepper)



Menu 3

Breakfast

Veggie and ham omelet (eggs, heavy cream, salt, green pepper, ham, butter, shredded cheddar/Monterey jack cheese) with sour cream, guacamole and salsa.



Lunch

Cobb salad (lettuce, shredded cheddar/Monterey jack cheese, tomatoes, bacon, chicken tenders, hard-boiled egg, ranch dressing and salt)



Dinner

Baked Dijon salmon (salmon, mayonnaise, Dijon mustard, parmesan cheese, salt) with green beans almandine (green beans, almonds, butter and salt)



Menu 4

Breakfast

Cauliflower scrambled eggs (eggs, butter, green peppers, cauliflower, butter, salt and shredded cheddar/Monterey jack cheese) and turkey sausage



Lunch

Cheeseburger (beef, butter, salt, pepper, American cheese) on a bed of lettuce with spicy sauce (mayonnaise, canola oil, hot sauce, sugar and soy sauce)



Dinner

Chicken and broccoli zucchini pasta alfredo (zucchini spirals, alfredo sauce, heavy cream, butter, salt, chicken breast and broccoli) and a side of sunflower seeds



Menu 5 (Chamber)

Breakfast

Spinach, tomato and cheese omelet (egg, heavy cream, salt, spinach, tomatoes, butter and American cheese) with whole milk



Lunch

Entrée chicken salad (lettuce, shredded cheddar/Monterey jack cheese and tomatoes; chicken breast, mayonnaise, celery, carrots and salt)



Dinner

Beef stir fry (beef roast, broccoli, green pepper, onion, soy sauce, canola oil, salt and peanuts) with cauliflower rice



Menu 6 (Saturday)

Breakfast

Scrambled eggs (egg, heavy cream, butter, salt) and pork bacon



Lunch

Broccoli and chicken gratin (broccoli, cream cheese, butter, heavy cream, garlic, salt, chicken breast and parmesan cheese) served over buttered cauliflower rice



Dinner

Entrée steak salad (lettuce, avocado, green pepper, carrots, tomatoes, sunflower seeds, grilled beef roast, ranch dressing and salt)



Menu 7 (Sunday)

Breakfast

Zucchini scramble (zucchini spirals, parmesan cheese, egg, onion powder, garlic, salt and butter)



Lunch

Stuffed pepper casserole (ground beef, onion, butter, green pepper, salt, crushed tomatoes and flaxseed) over cauliflower rice and topped with shredded cheddar/Monterey jack cheese



Dinner

Egg salad (hard-boiled eggs, mayonnaise, Dijon mustard, celery, paprika and salt) on a bed of lettuce



Snacks

Pecans; salted, dry roasted peanuts



Plant-based, Low-Fat Diet Menu

Menu 1

Breakfast

Cinnamon, brown sugar and blueberry quinoa (quinoa, ground cinnamon, brown sugar, salt, blueberries)



Lunch

Black bean stir fry (black beans, garlic, tomatoes, salt, onions and spinach) over basmati rice with apple slices (lemon juice to prevent browning)



Dinner

Spaghetti with vegan pasta sauce (marinara sauce, broccoli, green peppers, chickpeas and salt)



Menu 2

Breakfast

Hummus bagel sandwich (plain bagel, hummus, spinach, onions) with soy milk and raisins



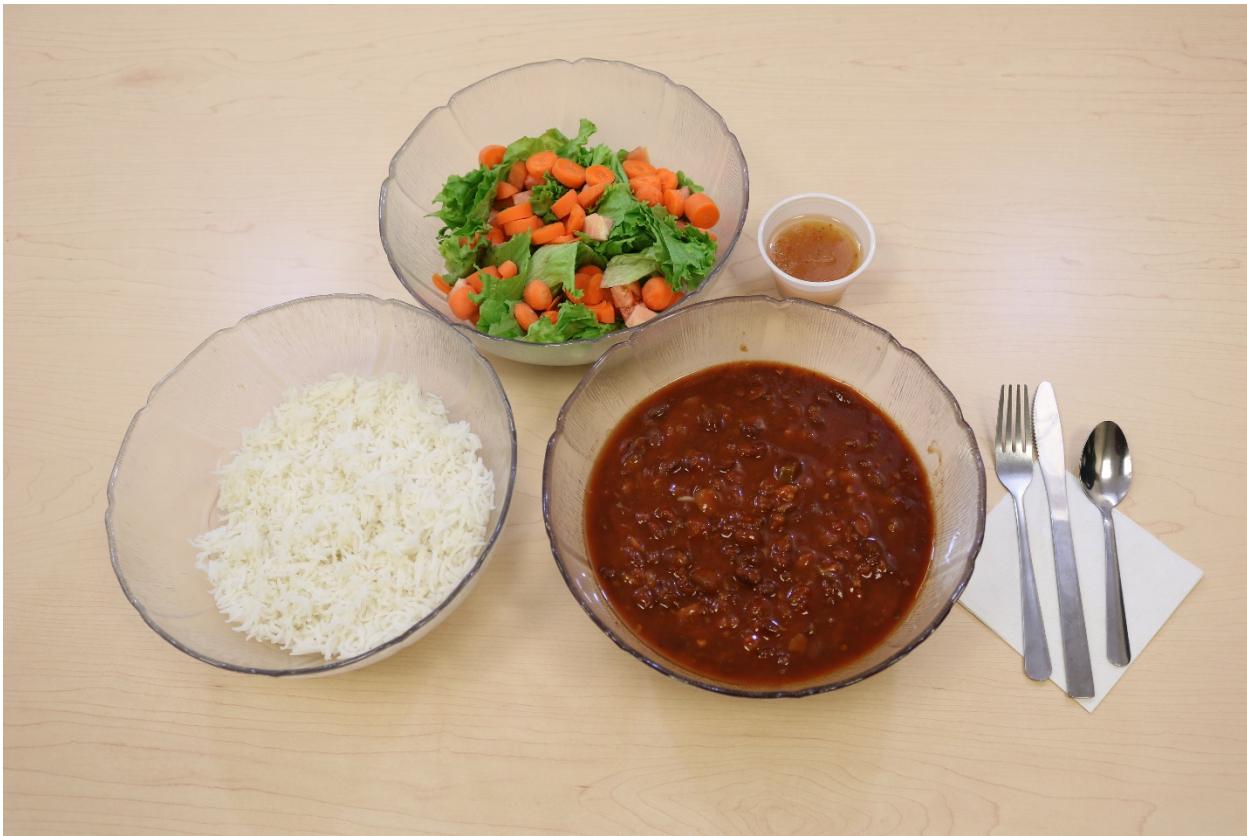
Lunch

Stuffed baked potatoes (Idaho potatoes, salt, black beans, broccoli and salsa) with a side of grapes



Dinner

Vegetarian chili with salted basmati rice and a side salad (lettuce, tomato, carrot) with fat-free Italian dressing



Menu 3

Breakfast

Cranberry vanilla quinoa (quinoa, salt, dried sweetened cranberries and vanilla soy milk)



Lunch

Chickpea scramble (chickpeas, spinach, green peppers, white mushrooms, garlic, soy sauce, chili powder, cumin and salt) with oranges



Dinner

Black bean and mango tacos (flour tortillas, black beans, corn, mango, lemon juice and green pepper) with salsa, lettuce, tomatoes and a side of salted basmati rice



Menu 4

Breakfast

Blueberry oatmeal (instant oatmeal, salt, vanilla soy milk and blueberries) with bananas



Lunch

lentil and basmati rice soup (canned lentil soup with onions, carrots, celery, spinach and tomatoes and basmati rice)



Dinner

Baked, stuffed sweet potatoes (sweet potato, chickpeas, chili powder, salt and salsa) with broccoli and oranges



Menu 5 (Chamber)

Breakfast

Tofu scramble (firm tofu, onions, cauliflower, green peppers, nutritional yeast, garlic, black pepper and salt) with salsa and multigrain bread with strawberry jelly



Lunch

Penne with vegan burger sauce (penne pasta, crushed tomatoes, green peppers, mushrooms, onions and vegan burger) with grapes



Dinner

Burrito bowl (basmati rice, black beans, salt, corn, green peppers, onions and lemon juice) with salsa and apple slices (lemon juice to prevent browning)



Menu 6 (Saturday)

Breakfast

Apple, raisin oatmeal (instant oatmeal, salt, applesauce and raisins) with Soy yogurt and canned peaches



Lunch

Tofu stir-fry (firm tofu, broccoli, sweet potato, nutritional yeast, green peppers and soy sauce) over basmati rice with a side of oranges



Dinner

Hummus sandwich (whole wheat bread, hummus, tomatoes, cucumber slices and spinach) with pretzel twists and apple slices (lemon juice to prevent browning)



Menu 7 (Sunday)

Breakfast

Peanut butter yogurt (vanilla soy yogurt with PB2 and Splenda), multigrain toast, grape jelly and bananas



Lunch

Lentil soup (canned lentil soup with rice, broccoli, sweet potato, spinach and garlic added) and grapes



Dinner

Pasta salad (penne pasta, fat-free Italian dressing, tomatoes, green peppers, black olives and onions) with apple slices (lemon juice to prevent browning)



Snacks

Dried apricots, raisins and dried edamame

