Practice-Based Research Results with Proprietary Medical Food: Effects on Plasma Lipid Profile and Selected Clinical Biomarkers for Metabolic Syndrome

BACKGROUND

Dyslipidemia is a group of conditions marked by abnormal levels of blood lipids or lipoproteins, such as elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C), raised triglycerides (TGs), and reduced high-density lipoprotein cholesterol (HDL-C). According to the National Health and Nutrition Examination Survey (NHANES 2003-2006), 53% (105.3 million) of U.S. adults have lipid abnormalities.[1]

Dyslipidemia is a prominent risk factor for atherosclerotic cardiovascular disease (CVD). Elevated LDL-C is a well-established risk factor.[2] Among the LDL-C subclasses that differ in size and density, the small dense LDL-C is more prone to oxidative modification and thus particularly atherogenic.[3,4] High TGs and low HDL-C are also independent predictors of CVD.[5] Aspects of dyslipidemia are part of the established diagnostic criteria for metabolic syndrome (plasma TGs ≥ 150 mg/dL and HDL-C < 40 mg/dL in men or < 50 mg/dL in women) along with elevated waist circumference (WC), blood pressure (BP), and fasting plasma glucose level.[6] If present, metabolic syndrome considerably increases the risk for CVD and type II diabetes (T2D) and should be managed appropriately. In this population, management of atherogenic plasma lipid profile, in addition to other clinical risk factors such as BP, inflammation, and oxidative stress—as well as overweight and obesity—is essential to reduce the risk of future disease and disease burden.[6]

In individuals with dyslipidemia, metabolic syndrome, or CVD, lifestyle-based interventions are essential in management of lipid abnormalities and halting progression towards advanced cardiovascular and metabolic disease.[6,7] The Proprietary Medical Food was developed to reflect current recommendations from the National Cholesterol Education Program, the American Heart Association, and Academy of Nutrition and Dietetics for dietary management of dyslipidemia. These recommendations include a dietary source of plant-derived omega-3 fatty acids through daily intake of α-linolenic acid (ALA) at 1.6 g for men and 1.1 g for women, ensuring 25% to 35% of daily energy comes from dietary fat and <7% of overall daily energy from saturated fat, dietary cholesterol intake <200 mg/day, 10 g to 20 g/day of soluble fiber, and importantly, inclusion of sources of antioxidants and efficacious doses of plant sterols/stanols.[2,6,8-11]

Medical foods deliver macro- and micronutrients, as well as key ingredients that are targeted for the nutritional management of a specific condition. Previous studies have shown that use of a medical food may provide benefits to plasma lipids beyond that of diet alone.[12,13]

OBJECTIVE

The primary objective of this multi-site, prospective case series was to measure changes in plasma atherogenic lipid profile and metabolic syndrome-related variables from baseline to 4 weeks after daily consumption of Proprietary Medical Food (either soy or pea/rice protein version) in subjects with dyslipidemia. The secondary objective was to evaluate change in these variables between baseline and 8 weeks in a subgroup of these participants.

RESULTS

A total of 24 participants were enrolled from 3 study sites. Baseline characteristics are summarized in **Table 1**. Twenty-one subjects completed 4 weeks (n=12 pea/rice, n=9 soy), and blood work is available for 19 subjects (n=11 pea/rice, n=8 soy). A subgroup of 12 participants continued and completed the 8-week evaluation (n=9 pea/rice, n=3 soy). No adverse events were reported.

Table 1. Baseline Characteristics of the 24 Study Participants

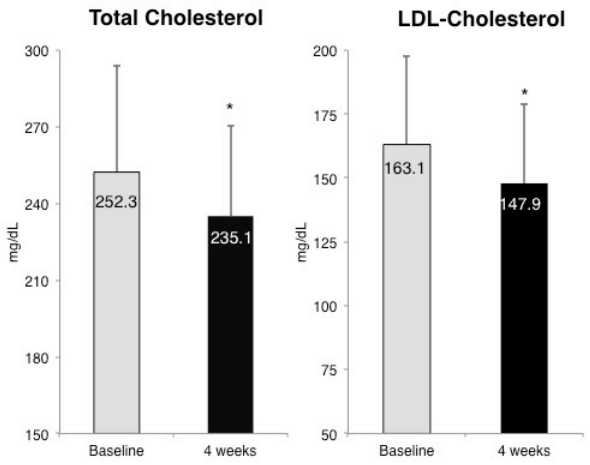
Sex	
Women	17
Men	7
Age (y)	
Mean ± SD	51.5 ± 9.6
Range	34 to 67
Race and ethnicity	
Caucasian	22
Asian	2
Proprietary Medical Food version	
Pea/rice protein	13
Soy protein	11
Weight (lb.)	
Mean ± SD	201.3 ± 36.8
Range	129 to 283
BMI (kg/m^2)	
Mean ± SD	33.0 ± 6.2
Range	22.9 to 50.1
WC (inches)	
Mean ± SD	40.7 ± 4.7
Range	30.8 to 49.0

Significant Decrease in Atherogenic Lipid Profile, Resulting in Reclassification into Lower Risk Categories at 4 Weeks

After 4 weeks, TC showed a statistically significant reduction from baseline (252.3 ± 41.5 mg/dL) to 4 weeks (235.1 ± 35.4 mg/dL; **Figure 1**)—an average 6.2% reduction leading to a clinical reclassification of risk score from high (≥ 240 mg/dL) to borderline high (200 mg/dL to 239 mg/dL).[2] Spearman correlation analysis showed that change in TC levels at 4 weeks was significantly associated with baseline TC levels, indicating that subjects with higher baseline TC experienced greater reduction (rho=-0.54; p=0.017). No significant difference was seen between the change in the soy and the pea/rice groups.

Similarly, LDL-C was significantly reduced from baseline (163.1 ± 34.4 mg/dL) to 4 weeks (147.9 ± 31.1 mg/dL; **Figure 1**), an average 8.5% reduction. Overall, the group reclassified LDL risk score from high (160 mg/dL to 189 mg/dL) to borderline high (130 mg/dL to 159 mg/dL) during the 4-week intervention.[2] No significant difference was seen between the change in the soy and the pea/rice groups.

On average, participants had a weight reduction of 1.5 ± 1.4 lb. at 4 weeks. Spearman correlation analyses showed that changes in TC and LDL-C were not significantly correlated with body weight changes, reflective of the delivery of lipid lowering actives in the formula (rho=0.09, p=0.72 for TC; rho=-0.04, p=0.89 for LDL-C).



* Statistically significant.

Figure 1. Significant changes in TC and LDL-C levels at 4 weeks compared with baseline (mean ± SD; n=19).

Apolipoprotein B (apo B), the main protein in LDL-C aiding in the transport of LDL-C in the bloodstream and the uptake of cholesterol into cells, was measured in select participants. Apo B concentrations in plasma were significantly reduced, with an average of 8.2% reduction within 4 weeks (p=0.038) (**Table 2**). Non-HDL cholesterol (non-HDL-C), a strong marker of CVD risk,[14] was significantly reduced within 4 weeks (**Table 2**), with an average reduction of 8.6% (p=0.041).

Table 2. Significant Reduction in Biomarkers of Atherogenic Lipid Profile within 4 Weeks

Variable	N	Level
Apo B (mg/dL)	7	Baseline: 140.4 ± 37.4 4 weeks: **127.9 ± 28.6*** *Goal: <90*[†]
non-HDL-C (mg/dL)	12	Baseline: 125.8 ± 15.3 4 weeks: **117.7 ± 13.7*** *Goal: <130*

* Statistically significant.
[†] From ADA/ACC Consensus Report Treatment Goals.[15]

Biomarkers of Metabolic Syndrome and Cardiometabolic Risk Were Reduced within 4 Weeks

At 4 weeks, a statistically significant change was seen in WC and systolic BP (**Table 3**). HDL-C and glucose levels were comparable at baseline and at 4 weeks, and remained within the normal range throughout. There was a trend towards a decrease (by an average 3.3% reduction) in plasma TGs.

Table 3. Metabolic Syndrome Criteria at Baseline and at 4 Weeks

Variable	N	Level
WC (inches)	21	Baseline: 40.5 ± 4.7 4 weeks: **39.7 ± 4.5*** *Criteria: >40 (m), >35 (w)*[†]
SBP (mmHg)	21	Baseline: 125.8 ± 15.3 4 weeks: **117.7 ± 13.7*** *Criteria: ≥130*
HDL-C (mg/dL)	18	Baseline: 60.0 ± 17.2 4 weeks: 60.5 ± 17.2 *Criteria: <40 (m) <50 (w)*
TGs (mg/dL)	18	Baseline: 144.7 ± 65.4 4 weeks: 136.0 ± 67.2 *Criteria: ≥150*
Glucose (mg/dL)	19	Baseline: 95.7 ± 13.0 4 weeks: 96.8 ± 15.2 *Criteria: ≥100*

* Statistically significant from baseline (p<0.05) as assessed by paired t-tests between time points. Sample size varied due to missing data.
[†] From AHA/NHLBI Scientific Statement.[6]

High sensitivity C-reactive protein (hs-CRP) was measured in 7 participants. The hs-CRP level was 9.13 ± 12.59 mg/L at baseline and 4.43 ± 2.37 mg/L at 4 weeks. Although this reflected a trend in improvement, it was not statistically significant (p=0.357) due to sample size and large variations.

Assessment of 3-day dietary diaries indicated that compared with baseline, caloric intake was comparable (ANOVA p=0.149). Proportion of energy from fat, protein, and carbohydrate also remained comparable across the study at a whole-group level, with the proportion of energy coming from protein, carbohydrate and fat consistent (at ~25%, 40%, and 35%, respectively) across the 4 weeks (p=0.724; p=0.980, p=0.780, respectively). The proportion of energy coming from saturated fat, polyunsaturated fat, and monounsaturated fat remained at ~10%, 8%, and 15% (p=0.959; p=0.778; p=0.390, respectively). An increase in intake of ALA (as % total energy) approached significance across the groups compared with baseline intake prior to medical food intervention (p=0.077). Baseline intakes of fiber were low at 13.3 g/day, and increased to 22 g to 23 g/day with the inclusion of Proprietary Medical Food in the diet (p<0.05). Similarly, significant increases were seen in micronutrient intake of magnesium, selenium, zinc, folate, thiamin, riboflavin, niacin, and vitamins A, B_6, B_{12}, D, and E
(p<0.05 for all nutrients listed).

Further Reduction in Atherogenic Lipid Profile at 8 Weeks: a Subgroup Analysis

After 4 weeks, 12 participants continued to consume Proprietary Medical Food to visit 3 (8 weeks). Compared with baseline, a statistically significant reduction was seen in TC (-6.4%), LDL-C (-10.0%), and WC (-2.0%; **Table 4**). Spearman correlation analyses found that the magnitude of change in TC, LDL-C, and WC were not correlated with body weight change during the study (p>0.05). No further significant change was seen in SBP, HDL, TGs, or glucose from baseline to 8 weeks. Magnitude of change was similar in Proprietary Medical Food soy and pea/rice protein groups.

Table 4. Atherogenic Lipid Parameters and Metabolic Syndrome Criteria in Subjects Completing the 8-week Intervention (N=12)

Variable	Level
TC (mg/dL)	Baseline: 249.3 ± 30.0 8 weeks: **232.4 ± 25.1***
LDL-C (mg/dL)	Baseline: 162.2 ± 26.0 8 weeks: **145.3 ± 23.9***
WC (inches)	Baseline: 42.0 ± 4.3 8 weeks: **41.1 ± 4.2***

* Statistically significant from baseline as assessed by paired t-tests between time-points (p<0.05).

CLINICAL REVIEW OF 2 INDIVIDUAL CASES

Case 1

History & Physical Findings

The first case was a 59 y/o Caucasian woman with dyslipidemia (elevated TC and LDL-C). She was obese (BMI 41.0 kg/m^2, WC 43.5 inches) and diagnosed with hypertension (140/98 mm Hg). Prior to the study, she had been taking an angiotensin converting enzyme inhibitor (ACEI, as lisinopril) for hypertension and omeprazole for heartburn. She also reported taking a vitamin B complex nutritional supplement.

Nutritional Management Plan

Management plan was to begin medical nutrition therapy with Proprietary Medical Food (pea/rice protein version) at 2 servings per day. Basic guidance on inclusion of the medical food in a normal meal pattern was provided.

Progress at 8 Weeks

Over the 8 weeks, the participant reported satisfaction with the consumption of the study product. No changes in her physical activity were made, though she reported reduction in sugar and carbohydrate intake and stated tracking dietary intake was a useful motivating tool. The nutritional intervention had no negative impact in self-reported health assessment/quality of life as assessed by the SF-12 instrument (score remained at 31 throughout the 8-week period).[16] Changes in various outcomes are summarized in **Table 5**.

Compared with baseline, there was a reduction in pro-atherogenic lipid profile (TC, TGs, LDL-C, and apo B) at 8 weeks; TC had reduced to within normal range, whereas LDL-C reclassified to “near optimal” according to NCEP-ATP III classification. Cholesterol/HDL also fell within optimal range during the intervention. Overall, medical nutrition therapy including Proprietary Medical Food had a beneficial impact on multiple metabolic markers within 8 weeks.

Table 5. Changes in Metabolic Variables from Baseline to 8 Weeks in Case 1

	Reference value	Baseline	4 weeks	8 weeks
Weight (lb.)		228	218	217
WC (inches)		43.5	43	43
BP (mmHg)	*<130/85*	140/98	130/92	138/84
TC (mg/dL)	*<200*	225	185	190
TGs (mg/dL)	*<150*	112	77	71
LDL-C (mg/dL)	*<100*	153	116	125
HDL-C (mg/dL)	*>50*	58	54	56
non-HDL-C (mg/dL)	*<130*	167	131	134
Cholesterol/HDL	*<3.5*	3.9	3.4	3.4
apo B (mg/dL)	*<80*	94	-	86
Glucose (mg/dL)	*<100*	94	88	85

Case 2

History & Physical Findings

The second case was a 51 y/o overweight Caucasian man (BMI 25.1, WC 35 inches) diagnosed with dyslipidemia (elevated TC and LDL-C) for over 20 years. His BP was 108/78 mm Hg. He has family history of hyperlipidemia. He had never taken lipid-lowering medication, but had taken a red yeast rice dietary supplement in the past.

Nutritional Management Plan

Management plan was to begin medical nutrition therapy with Proprietary Medical Food (soy protein version) at 2 servings per day.

Progress at 4 Weeks

Changes in various outcomes are summarized in **Table 6**. Compared with baseline, there were improvements in his serum lipids: TC was reduced from "high" to nearly "normal," LDL-C from "very high" to "near optimal," and cholesterol/HDL fell within a normal range. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a marker used to indicate vascular inflammation, also fell within a normal range at 4 weeks.

Additional cardiovascular risk markers, including LDL particle number and LDL particle size, were measured in Case 2 (**Table 7**). Compared with baseline, improvements were seen in LDL particle number: from high (reference range: >1538 nmol/L) to moderate (reference range: 1260 nmol/L to 1538 nmol/L), and small LDL particle from high (reference range: >217 nmol/L) to moderate (reference range: 162 nmol/L to 217 nmol/L) at 4 weeks.

The subject reported that he was "very satisfied" with consuming the Proprietary Medical Food and enjoyed the taste. He maintained exercise patterns throughout the study and made no changes during the study period. The subject reported compliance with 2 servings of the medical food each day, and also reported eating less red meat and including more foods—such as whole grains, beans, peas, and legumes—in his meal pattern.

Table 6. Changes in Metabolic Variables from Baseline to 4 Weeks in Case 2

	Reference value	Baseline	4 weeks
Weight (lb.)		185	187
WC (inches)		35	35
BP (mmHg)	*<135/85*	108/78	94/62
TC (mg/dL)	*<200*	279	202
TGs (mg/dL)	*<150*	93	60
LDL-C (mg/dL)	*<100*	198	129
HDL-C (mg/dL)	*>40*	62	63
non-HDL-C (mg/dL)	*<130*	217	142
Cholesterol/HDL	*<3.5*	4.5	3.4
apo B (mg/dL)	*<80*	140	-
Glucose (mg/dL)	*<100*	80	82
Lp-PLA2 (ng/mL)	*<200*	251	195

Table 7. Changes in Additional Cardiovascular Risk Markers from Baseline to 4 Weeks in Case 2

	Reference value	Baseline	4 weeks
LDL particle number (nmol/L)	*<1260*	1897	1388
LPL particle size			
Small (nmol/L)	*<162*	260	186
Medium (nmol/L)	*<201*	484	304

SUMMARY

Dyslipidemia is a prominent risk factor for atherosclerotic CVD and needs to be carefully tracked and managed in high risk groups, such as those with metabolic syndrome. In this practice-based research study, patients with dyslipidemia across 3 independent clinical sites were placed on 2 servings of Proprietary Medical Food per day with minimal changes in other dietary habits across the whole subject cohort, and no prescribed change in the amount of physical activity. At the end of 4 weeks, significant changes were seen in the atherogenic lipid profile, with significant reduction in total and LDL-C and apo B. In select cases where particle size was measured, these were further indication of improvements in overall lipid profile risk.

Improvements in metabolic syndrome-related variables were seen, highlighting potential for broader support for cardiometabolic patients. According to a meta-regression analysis of cohort studies, each 1 cm reduction in waist circumference indicates a 2% reduction in CVD risk.[17] In this study, the magnitude of change seen in 4 weeks would therefore correspond to a 4% reduction in CVD risk. Although on a whole group level this was a normotensive group, the magnitude of reduction corresponds to a 12.8% CVD risk reduction based on data from hypertensive populations.[18]

The development of dyslipidemia and associated chronic conditions are commonly attributed to lifestyle choices; multiple national organizations recommend lifestyle modifications including a dietary plan (e.g. a Mediterranean-style diet) and physical activity as the foundation of treatment of these metabolic abnormalities. Two previous clinical studies, have shown that a 12-week intensive diet and lifestyle intervention resulted in mean LDL-C reduction of 8.4% and 8.8%, respectively, and the addition of medical food enhances LDL-C reduction to 17.3% and 16.7%, respectively.[12,13] In this multi-site study, Proprietary Medical Food alone showed a 10% reduction in LDL-C in 8 weeks, with additional positive changes in atherogenic lipid profile and cardiometabolic risk biomarkers within 4 weeks.

In clinical practice, an additional emphasis on combining a medical food such as Proprietary Medical Food with dietary and lifestyle recommendations can bring broad benefit. This combination can form the basis of a medical nutrition therapy program for longer-term management of cardiometabolic health for individual patients.

METHODS/DESIGN

Participants

Participants were overweight (BMI>25 kg/m^2) men and women ages 24 y/o to 65 y/o with documented dyslipidemia; some also had metabolic syndrome. Dyslipidemia was defined as: TC>220 mg/dL and/or LDL-C>135 mg/dL. Metabolic syndrome was defined as having met the ATP III criteria, defined as any of the 3 following: WC>40 in (men) and 35 in (women); fasting blood glucose>100 mg/dL; BP>130/85 mm Hg; HDL-C< 40 mg/dL (men) and < 50 mg/dL (women). Main exclusion criteria included (1) use of lipid-lowering drugs or anticoagulant medications within 4 weeks prior to the study, (2) history of renal, hepatic, and autoimmune disease, (3) history of cancer, AIDS, deep vein thrombosis or pulmonary embolus, (4) pregnancy or breastfeeding, and (5) use of alcohol within 24 hours of the evaluation visits. The study was carried out in compliance with the Helsinki Declaration of 1975, and the study was approved by Quorum Independent Review Board (Seattle, WA). Informed written consent was obtained from all participants prior to enrollment in the study.

Study Design

This open-label, case observation series was conducted at 3 sites: Meridian Naturopathic Clinic and Assessment Center (Mississauga, Canada), Whole Health Associates, LLC (Avon, CT), and WholeHealth Chicago, the Center for Integrative Medicine (Chicago, IL) under the guidance of the Functional Medicine Research Center® (Gig Harbor, WA), the clinical research arm of Metagenics, Inc.

At baseline (Visit 1), participants were instructed to begin 2 servings daily of the Proprietary Medical Food incorporated into their meal pattern. Two versions of Proprietary Medical Food were used in the study: (1) a soy protein version and (2) a pea and rice protein version. Each participant consumed only 1 version of the medical food during the study. The nutritional profile of Proprietary Medical Food is summarized in **Table 8**.

Participants returned to the clinic at Week 4 (Visit 2) and a subgroup returning at Week 8 (Visit 3) for clinical evaluation and assessment for compliance and adverse events. An overview of clinical visits is summarized in **Table 9**. Dietary intakes were tracked throughout the study on a weekly basis using a 3-day food diary (2 weekdays and 1 weekend day). Nutritional analysis of these dietary intakes was completed by a registered dietitian using the US Department of Agriculture (USDA) Supertracker (https://www.supertracker.usda.gov), and the nutritional composition of the Proprietary Medical Food was added.

Table 8. Nutritional Profile Summary of Proprietary Medical Food

Soy protein version

Information per serving	
Serving Size	2 scoops (38 g)
Calories	140
Total Fat	5 g
Saturated Fat	1 g
Trans Fat	0 g
Polyunsaturated Fat	1 g
Monounsaturated Fat	2.5 g
Cholesterol	0 mg
Sodium	110 mg
Potassium	180 mg
Total Carbohydrate	12 g
Dietary Fiber	5 g
Sugars	4 g
Protein	13 g[†]
[†]15 g total protein with added amino acids: L-leucine, L-isoleucine, L-lysine, and L-valine	

Ingredients: Soy protein isolate, isomalto-oligosaccharide, natural flavors, high oleic sunflower oil, organic cane sugar, Dutch processed cocoa powder, flaxseed, phytosterols, L-lysine HCl, L-leucine, silica, magnesium citrate, L-valine, guar gum, protein matrix and polyphenols from hops extract, vitamin and mineral blend (zinc gluconate, ascorbic acid, manganese gluconate, d-alpha tocopheryl acetate, copper gluconate, D-biotin, retinyl palmitate, niacinamide, cholecalciferol, d-calcium pantothenate, chromium picolinate, pyridoxine HCl, riboflavin, potassium iodide, thiamin HCl, methylcobalamin, calcium L-5-methyltetrahydrofolate, and selenomethionine), L-isoleucine, dicalcium phosphate, xanthan gum, and Luo Han Guo (monk fruit) extract.

Pea/rice protein version

Information per serving	
Serving Size	2 scoops (39 g)
Calories	150
Total Fat	5 g
Saturated Fat	1 g
Trans Fat	0 g
Polyunsaturated Fat	1 g
Monounsaturated Fat	2.5 g
Cholesterol	0 mg
Sodium	130 mg
Potassium	90 mg
Total Carbohydrate	14 g
Dietary Fiber	5 g
Sugars	4 g
Protein	13 g[†]
[†]15 g total protein with added amino acids: L-leucine, L-isoleucine, L-lysine, and L-valine	

Ingredients: Pea protein isolate, isomalto-oligosaccharide, natural flavors, rice protein concentrate, organic cane sugar, high oleic sunflower oil, flaxseed, L-lysine HCl, phytosterols, L-leucine, silica, magnesium citrate, L-valine, guar gum, protein matrix and polyphenols from hops extract, vitamin and mineral blend (zinc gluconate, ascorbic acid, manganese gluconate, d-alpha tocopheryl acetate, copper gluconate, D-biotin, retinyl palmitate, niacinamide, cholecalciferol, d-calcium pantothenate, chromium picolinate, pyridoxine HCl, riboflavin, potassium iodide, thiamin HCl, methylcobalamin, calcium L-5-methyltetrahydrofolate, and selenomethionine), L-isoleucine, dicalcium phosphate, Luo Han Guo (monk fruit) extract, and xanthan gum.

Table 9. Clinical Visit Overview

Visit 1 (Week 0)	• Obtain informed consent • Fasting blood collection, physical measurements, and clinical examination • Education on study protocol • Provide study product • Assess baseline diet and lifestyle via a questionnaire
Visit 2 (Week 4)	• Fasting blood collection, physical measurements, and clinical examination • Refresh education on study protocol • Provide study product • Assess diet and lifestyle via a questionnaire • Physician summary of suspected adverse events, and reported outcomes
Visit 3 (Week 8)	• Fasting blood collection, physical measurements, and clinical examination • Assess diet and lifestyle via a questionnaire • Physician summary of suspected adverse events, and reported outcomes

Laboratory Analysis

Fasting blood samples obtained at each clinic visit were analyzed for lipid profile (TGs, TC, LDL-C, HDL-C, and apo B). Additionally, particle size was measured in select subjects. Glucose and hs-CRP were measured in all subjects, and additional markers, such as Lp-PLA_2, were measured in select subjects.

Statistical Analyses

Paired t-tests were performed to assess differences in primary and secondary outcome measures from baseline to Week 4 and from baseline to Week 8. Unpaired t-tests were performed to determine differences in outcome measures between the 2 versions of Proprietary Medical Food. A 2-sided value of $P<0.05$ was considered statistically significant. Spearman's rank correlation coefficient was used to explore relationships between variables. One-way analysis of variance (ANOVA) was used to explore differences in reported nutrient intakes, with Tukey's HSD used to determine specific post-hoc between-group differences where a significant ANOVA result was achieved.

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