

The Effect of a Plant-Based Low-Carbohydrate (“Eco-Atkins”) Diet on Body Weight and Blood Lipid Concentrations in Hyperlipidemic Subjects

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Background: Low-carbohydrate, high-animal protein diets, which are advocated for weight loss, may not promote the desired reduction in low-density lipoprotein cholesterol (LDL-C) concentration. The effect of exchanging the animal proteins and fats for those of vegetable origin has not been tested. Our objective was to determine the effect on weight loss and LDL-C concentration of a low-carbohydrate diet high in vegetable proteins from gluten, soy, nuts, fruits, vegetables, cereals, and vegetable oils compared with a high-carbohydrate diet based on low-fat dairy and whole grain products.

Methods: A total of 47 overweight hyperlipidemic men and women consumed either (1) a low-carbohydrate (26% of total calories), high-vegetable protein (31% from gluten, soy, nuts, fruit, vegetables, and cereals), and vegetable oil (43%) plant-based diet or (2) a high-carbohydrate lacto-ovo vegetarian diet (58% carbohydrate, 16% protein, and 25% fat) for 4 weeks each in a parallel study design. The study food was provided at 60% of calorie requirements.

Results: Of the 47 subjects, 44 (94%) (test, n=22 [92%]; control, n=22 [96%]) completed the study. Weight loss was similar for both diets (approximately 4.0 kg). However, reductions in LDL-C concentration and total cholesterol-HDL-C and apolipoprotein B-apolipoprotein AI ratios were greater for the low-carbohydrate compared with the high-carbohydrate diet (−8.1% [$P=.002$], −8.7% [$P=.004$], and −9.6% [$P=.001$], respectively). Reductions in systolic and diastolic blood pressure were also seen (−1.9% [$P=.052$] and −2.4% [$P=.02$], respectively).

Conclusion: A low-carbohydrate plant-based diet has lipid-lowering advantages over a high-carbohydrate, low-fat weight-loss diet in improving heart disease risk factors not seen with conventional low-fat diets with animal products.

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THERE IS A DILEMMA RELATING to the proportion and source of fat, protein, and carbohydrate that constitutes the optimal weight loss and cholesterol-lowering diet. Newer dietary approaches for the prevention and treatment of chronic disease increase the consumption of fruit and vegetables but reduce meat consumption either directly as part of the dietary strategy¹ or displace meat by advocating increased intakes of fish, poultry, and low-fat dairy foods.²⁻⁴

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Running counter to this advice has been the promotion of low-carbohydrate diets with increased meat consumption for body weight reduction and also in the longer term for the prevention and treatment of diabetes and coronary heart disease

(CHD). These diets not only challenge the concept that red meat intakes should be reduced but also reverse the dietary macronutrient profile with fat and protein as the major macronutrients and carbohydrates as the minor macronutrient. Such low-carbohydrate diets have been shown to be effective in inducing weight loss,^{1,5-8} reducing insulin resistance,⁷ lowering serum triglyceride (TG) concentrations, and raising high-density lipoprotein cholesterol (HDL-C) concentrations.^{1,5,6} However, the higher meat diets have not resulted in lower low-density lipoprotein cholesterol (LDL-C) concentrations, but have tended to increase LDL-C concentrations except when vegetarian sources of fat and protein were included.¹ This lack of a benefit for LDL-C control is a major disadvantage in using this dietary strategy in those already at increased risk of CHD.

In view of the apparent success of low-carbohydrate diets for weight loss and the

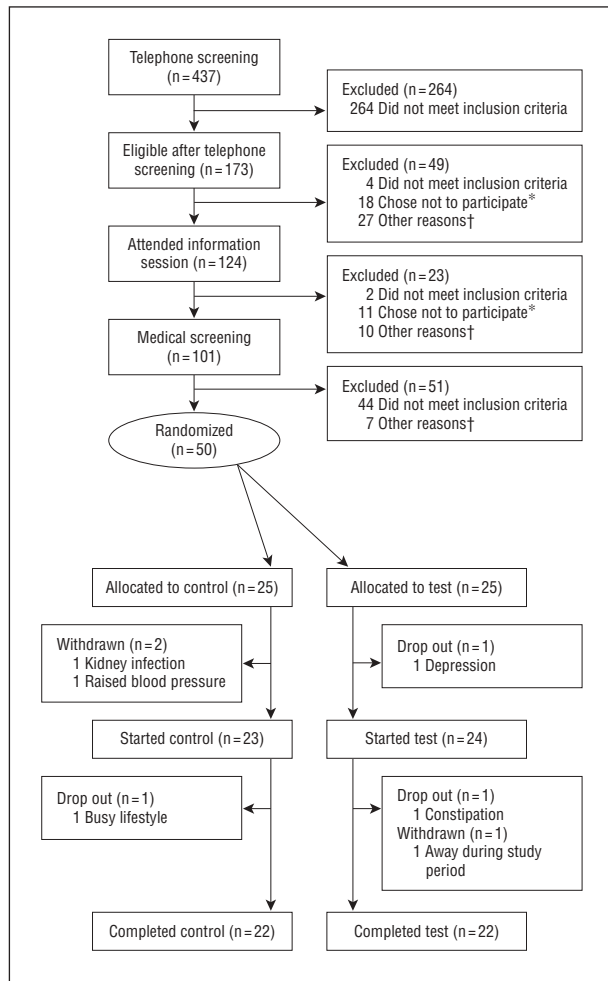


Figure 1. Patient flow diagram. *Chose not to participate (n=29): busy lifestyle (n=13), not interested (n=6), study too demanding (n=3), currently on another diet (n=2), no compensation (n=2), work-related reason (n=2), dislike prepackaged foods (n=1). †Other reasons (n=44): unable to contact (n=19), unable to come to clinic (n=13), away (n=5), throat surgery (n=1), bowel resection (n=1), high potassium concentration and blood pressure (n=1), high potassium concentration (n=1), elevated liver function test results (n=1), not interested (n=1), medical insurance issue (n=1).

demonstration that relatively high-carbohydrate diets low in animal products lower CHD risk factors,^{3,9-11} we determined the effect of a low-carbohydrate weight-loss diet, without the use of animal products, on serum lipid concentrations compared with a higher carbohydrate diet.

METHODS

PARTICIPANTS

Fifty overweight participants, recruited by newspaper advertisement and hospital clinic notices, were randomized, and 47 subjects were available to start the study. Of these, 44 (18 men and 26 postmenopausal women) completed the 1-month metabolic study (**Figure 1**). More than half the participants reported being of European origin (n=32 [northern, n=21; eastern, n=8; and southern, n=3]). The remainder had their origins in sub-Saharan Africa (n=4), the Indian subcontinent (n=4), Latin America (n=2), southeast Asia (n=2), and the Middle East (n=2). Four subjects did not provide their ethnic origins. Race was assessed by the participants using a classification provided by the

Table 1. Baseline Characteristics at Randomization for 50 Subjects^a

Characteristic	High-Carbohydrate Control Diet (n=25)	Low-Carbohydrate Test Diet (n=25)	P Value ^b
Age, y	56.1 (7.5)	57.8 (7.1)	.41
Male/female	12/13	10/15	.57
Body weight, kg	87.4 (11.7)	82.7 (11.1)	.15
BMI	31.0 (2.4)	30.6 (2.9)	.61
Blood pressure, mm Hg			
Systolic	126.1 (10.2)	127.7 (13.7)	.64
Diastolic	79.4 (8.1)	79.0 (7.7)	.86
Cholesterol, mg/dL			
Total	244 (43)	231 (60)	.39
LDL-C	166 (39)	153 (49)	.29
HDL-C	49 (11)	49 (15)	.90
Triglycerides, mg/dL	142 (73)	148 (87)	.80
Ratios			
TC-HDL-C	5.18 (1.42)	5.01 (1.60)	.70
LDL-C-HDL-C	3.51 (1.00)	3.33 (1.29)	.57
Glucose, mg/dL	93 (8)	97 (8)	.16
Exercise, METs ^c	16.7 (9.6)	24.0 (23.0)	.17
Medications, No. of subjects			
Lipid lowering (prior to start of study)	5	8	.33
Blood pressure	5	8	.33
Diabetes	0	0	...
Thyroid	2	1	.55

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; METs, metabolic equivalent of tasks; TC, total cholesterol.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555.

^aData are given as mean (SD) unless otherwise noted.

^bCalculated by the 2-sample *t* test or χ^2 test between high- vs low-carbohydrate diets.

^cBaseline data for control (n=23) and test (n=22).

investigators. Baseline characteristics of the participants are given in **Table 1**. Study inclusion criteria included healthy men and postmenopausal women between the ages of 21 and 70 years, with a high-normal or raised LDL-C concentration (>131 mg/dL [to convert to millimoles per liter, multiply by 0.0259] at diagnosis), TG concentration higher than 44 mg/dL (to convert to millimoles per liter, multiply by 0.0113) but lower than 442 mg/dL, a body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) higher than 27 and who were not currently involved in a weight-loss program. Exclusion criteria included lipid-lowering medications, hormone therapy, alcohol consumption of more than 2 drinks/d, tobacco use, major cardiovascular event or surgery in the preceding 6 months, diabetes, untreated hypothyroidism, blood pressure (BP) higher than 140/90 mm Hg, renal or liver disease, cancer (excluding non-melanoma skin cancer), or any food allergies. At recruitment, 13 subjects were taking lipid-lowering medications; however, these were discontinued at least 2 weeks prior to the start of the study after obtaining approval from their family physician. Thirteen participants were taking antihypertensive medications at a constant dose before and during the study. One participant altered the antihypertensive medication dosage during the study. Three participants took thyroxine at a constant dose before and during the study.

STUDY PROTOCOL

The intervention was a randomized parallel study stratified by sex in which participants were assigned to either low- or high-carbohydrate, calorie-reduced diets. The 1-month study was metabolically controlled with all food provided, and participants were seen at weekly intervals. At each visit, fasting body weights and BP were measured. Serum samples were obtained after 12-hour overnight fasts before treatment and at the end of weeks 2 and 4. Body weights were determined, with shoes removed and in indoor clothing, using a stationary beam balance scale (Healthometer; Continental Scale Corp, Bridgeview, Illinois). Blood pressure was measured 3 times in the non-dominant arm after sitting for 15 to 20 minutes using an automated digital BP machine (OMRON Healthcare Inc, Vernon Hills, Illinois). Food to be eaten by subjects for the entire metabolic month was prepacked and delivered to subjects by courier. A “no starch” high-protein nut bread was obtained from the clinic at weekly intervals. Participants were asked to hold exercise constant over the metabolic period. Exercise dairies were also completed weekly with type of exercise, duration, and intensity recorded as light, moderate, or vigorous in accordance with the Guidelines of the Centers of Disease Control and Prevention and the American College of Sports Medicine, and exercise was calculated as metabolic equivalent of tasks (METs).^{12,13} Body fat percentage was measured by bioelectrical impedance (Quantum II; RJL Systems, Clinton Township, Michigan) and waist and hip measurements were measured bi-weekly. Waist measurements were made at the umbilicus and hip measurements at the maximum lateral protrusion of the greater trochanter of the femur.

Subjects rated their overall feeling of satiety for the previous week at each study visit using a 9-point bipolar semantic scale, where -4 was extremely hungry, 0 was neutral, and +4 was uncomfortably full.¹⁰ Palatability was rated at the end of the study using a 7-point bipolar semantic scale, where -3 was very unpalatable, 0 was neutral, and +3 was very palatable.

The ethics committees of St Michael's Hospital and the University of Toronto, Ontario, Canada, and the Therapeutic Products Directorate of Health Canada approved the study. Written informed consent was obtained from the participants.

DIETS

Metabolically controlled diets in which all food was provided were consumed by the participants. The low-carbohydrate diet provided the minimum level of carbohydrates currently recommended (130 g/d)¹⁴ and eliminated common starch-containing foods, such as bread, baked goods, potatoes, and rice. The protein content was provided by gluten (54.8% of total protein), soy (23.0%), fruits and vegetables (8.7%), nuts (7.5%), and cereals (6.0%). Gluten was provided in the nut bread and wheat gluten (also called “seitan”) products and, together with soy, in burgers, veggie bacon, deli slices, and breakfast links. In addition, soy was provided as tofu and soy beverages. Nuts included almonds, cashews, hazelnuts, macadamia, pecans, and pistachios. The fat was provided by nuts (43.6% of total fat), vegetable oils (24.4%), soy products (18.5%), avocado (7.1%), cereals (2.7%), fruits and vegetables (2.3%), and seitan products (1.4%). The diet was designed to provide 26% of calories as carbohydrates, 31% as protein, and 43% as fat. The high-carbohydrate diet was a low-fat lacto-ovo vegetarian diet (58% carbohydrates, 16% protein, and 25% fat) using low-fat or skim milk dairy products and liquid egg whites or egg substitute to ensure a low-saturated fat and low-cholesterol intake.¹⁰ All diets were provided at 60% of estimated calorie requirements¹⁵ using the Harris-Benedict equation with allowance for exercise.^{16,17}

The low-carbohydrate diet featured viscous fiber-containing foods, including oats and barley, for the relatively limited amount of carbohydrates allowed, and the production of a “no starch” high-protein bread made entirely from ground almonds, hazel nuts, and wheat gluten. The carbohydrate foods and low-starch vegetables, emphasizing okra and eggplant, provided 6 to 7 g of viscous fiber per 2000-kcal diet.¹⁰ The bread was provided as part of the diet.

Food preparation by participants was made as straightforward as possible by the provision of commercial dishes or food items, which were ready for microwave or oven cooking or could be reconstituted with boiling water, as with instant soups. Diet foods were packed in a central location and shipped by courier in separate boxes for dry, refrigerated, and frozen goods. Egg substitutes and soy dairy foods were shipped in their commercial packages to be refrigerated on receipt by the participants.

With the low-carbohydrate diet, plant- or microbially derived vitamin and mineral supplements were also provided, including vitamin B₁₂, 1000 µg/wk (microbially synthesized B₁₂; Genestra Brands, Toronto, Ontario, Canada), and vitamin D (as vegan ergocalciferol), 200 IU/d (VegLife, Park City, Utah). Women were also provided with calcium, 500 mg/d, and magnesium, 250 mg/d (VegLife).

Self-taring electronic scales (My Weigh Scales, Vancouver, British Columbia, Canada, or Tanita Corporation, Arlington Heights, Illinois) were provided to all participants to weigh all food items consumed during the study and record the weights on the menu plan.

Adherence was assessed from the completed menu plans, and subjects were also requested to weigh any leftover food items. Subjects were asked to record the intake of prescribed vitamin and mineral supplements as a further measure of compliance throughout the study. Supplement bottles were returned at the end of the study. Participants were offered no financial compensation for participation in the study.

LABORATORY ANALYSES

Serum was analyzed according to the Lipid Research Clinics protocol¹⁸ for TC, TG, and HDL-C concentrations, after dextran sulfate-magnesium chloride precipitation (Bayer Technicon RA1000; Bayer Healthcare, Toronto)¹⁹ or by detergent solubilization and measurement of HDL-C (Roche Hitachi 917; Roche Diagnostics, Laval, Quebec, Canada), in the J. Alick Little Lipid Research Laboratory. Low-density lipoprotein cholesterol was calculated by the method of Friedewald et al²⁰ in millimoles per liter (LDL-C = total cholesterol [TC] - [TG/2.2 + HDL-C]).²⁰ Apolipoproteins AI (apo AI) and B (apo B) were measured by a nephelometric method (Dade Behring BN ProSpec; Dade Behring Canada Inc, Mississauga, Ontario). High-sensitivity C-reactive protein (hs-CRP) was measured by end-point nephelometry (Dade Behring BN ProSpec; Dade Behring Canada Inc). C-reactive protein values higher than 10 mg/L (to convert to nanomoles per liter, multiply by 9.524) were eliminated²¹ providing that they spiked more than 5 mg/L above the mean for the individual's series.

Blood glucose was measured in the hospital routine analytical laboratory by a glucose oxidase method (SYNCHRON LX Systems; Beckman Coulter Canada Inc, Mississauga). Insulin was measured by Access Ultrasensitive Insulin Assay, which is a simultaneous 1-step immunoenzymatic (“sandwich”) assay (Beckman Coulter Canada Inc). A measure of insulin resistance was derived for fasting glucose and insulin using the homeostasis model assessment-insulin resistance model: fasting glucose (in millimoles per liter) × insulin (in milliuunits per liter)/22.5.²² Hemoglobin A_{1c} (HbA_{1c}) was measured by a designated high-performance liquid chromatography method (Tosoh G7 Automated HPLC Analyzer; Tosoh Bioscience Inc, Grove City, Ohio).

Table 2. Nutritional Profiles at Baseline

Variable	High-Carbohydrate Control Diet	Low-Carbohydrate Test Diet	P Value ^a
Calories, mean (SE), kcal	1726.2 (113.8)	1779.0 (129.3)	.76
Total calories, % (SE)			
Available carbohydrate	46.4 (1.7)	45.0 (1.9)	.60
Protein	20.1 (0.8)	19.6 (0.9)	.68
Vegetable protein	5.9 (0.3)	5.7 (0.3)	.69
Soy protein	0.0 (0.0)	0.0 (0.0)	...
Fat	31.5 (1.5)	34.0 (1.6)	.25
Saturated	10.8 (0.7)	11.8 (0.8)	.36
Monounsaturated	12.5 (0.7)	12.9 (0.6)	.66
Polyunsaturated	5.5 (0.4)	6.4 (0.5)	.14
Alcohol	2.0 (0.8)	1.4 (0.7)	.53
Dietary fiber, mean (SE), g/1000 kcal	12.0 (0.9)	12.4 (1.1)	.76
Dietary cholesterol, mean (SE), mg/1000 kcal	144.2 (9.7)	152.4 (10.9)	.58

^aCalculated using the 2-sample *t* test between high- vs low-carbohydrate diets.

Diets were assessed for macronutrients, fatty acids, cholesterol, and fiber using a computer program based on the US Department of Agriculture database²³ and developed in our laboratory to allow the addition of the macronutrient content of study foods obtained from food labels or directly from food manufacturers.

STATISTICAL ANALYSES

The results are expressed as mean (SE). Serum lipid concentrations are expressed as absolute values in the Tables and percentage changes from baseline in the article text and Figures, unless otherwise stated. Differences between groups in baseline variables were assessed by the 2-sample *t* test (2 tailed). Intention-to-treat (ITT) analysis was undertaken with baseline observation carried forward for subjects who dropped out. Unless otherwise stated, ITT data are presented throughout. Time zero was used as the baseline. Within treatment groups, serum lipid concentrations and other measurements were not found to be significantly different between weeks 2 and 4 during the metabolic phase. For these reasons, the respective treatment differences were assessed by the CONTRAST statement in SAS²⁴ using all available data and reported as changes from baseline to weeks 2 and 4. The model specified change from baseline as the response variable with week as the main effect and baseline as covariate, except when percentage changes from baseline were assessed. A significant difference was found between weeks 2 and 4 for body weight and BMI; therefore, the end of treatment values were assessed with baseline observation carried forward using the General Linear Model in SAS.²⁴ Dietary data were analyzed using the 2-sample *t* tests for mean differences between the 2 treatment diets and at baseline.

RESULTS

Baseline characteristics, obtained at randomization, for the control and low-carbohydrate diets are provided in Table 1. No significant differences were found in any of the variables between the 2 groups. There were no significant differences in the mean macronutrient profiles between individuals assigned to the test and control diets at baseline (**Table 2**). Both diets were well complied with, with

Table 3. Nutritional Profiles During the Study

Variable	High-Carbohydrate Control Diet	Low-Carbohydrate Test Diet	P Value ^a
Calories, mean (SE), kcal	1488.2 (48.1)	1451.4 (47.3)	.59
Calorie compliance, % (SE)	94.2 (1.3)	94.8 (1.4)	.76
Total calories, % (SE)			
Available carbohydrate	58.2 (0.4)	26.8 (0.3)	<.001
Protein	16.8 (0.1)	30.0 (0.3)	<.001
Vegetable protein	7.0 (0.1)	29.9 (0.3)	<.001
Soy protein	0.2 (0.0)	6.8 (0.1)	<.001
Fat	24.5 (0.4)	43.1 (0.2)	<.001
Saturated	4.6 (0.0)	6.3 (0.1)	<.001
Monounsaturated	7.9 (0.2)	25.0 (0.2)	<.001
Polyunsaturated	9.1 (0.2)	9.6 (0.1)	.02
Alcohol	0.3 (0.2)	0.0 (0.0)	.15
Dietary fiber, mean (SE), g/1000 kcal	21.3 (0.2)	28.3 (0.2)	<.001
Dietary cholesterol, mean (SE), mg/1000 kcal	30.1 (1.4)	0.4 (0.3)	<.001

^aCalculated using the 2-sample *t* test between high- vs low-carbohydrate diets.

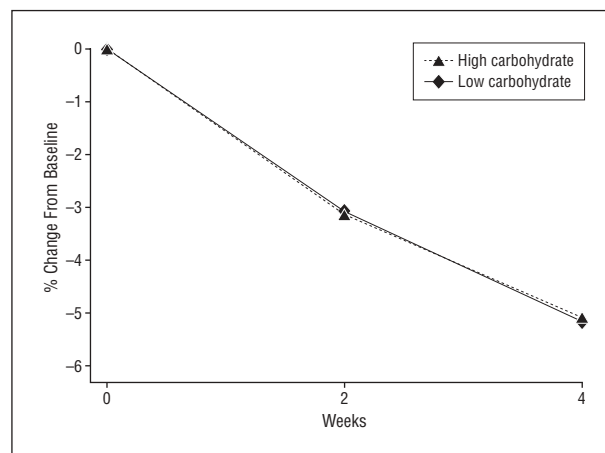


Figure 2. Weight loss from both diets during the 4 weeks of the study ($P=.98$) for completers.

no significant difference between treatments (**Table 3**). More than 90% of the calories provided were consumed for the test (95%) and control (94%) diets. Of those who started, all but 3 subjects completed the study: 2 withdrew from the control diet and 1 withdrew from the low-carbohydrate plant-based diet for reasons unrelated to the study protocol (Figure 1). The mean weight loss after 4 weeks of the metabolic phase was similar for both treatment diets at 4.7% (0.4%) (3.9 [0.4] kg) for the test and 4.9% (0.3%) (4.2 [0.3] kg) for the control ($P=.94$) diets. A similar pattern was seen with the completers (**Figure 2**). There were no absolute differences in calculated change in energy expenditure between the weeks 1 to 4 test and control treatments (-3.6 [2.7] vs 1.4 [1.7] METs; $P=.12$). Mean absolute subjective satiety ratings were significantly higher for the low-carbohydrate diet (1.5 [0.3] [low-carbohydrate diet] vs 0.8 [0.3] [high-carbohydrate diet]; $P=.003$). Satiety scores were positive for both treatments, indicating that the diets tended to satisfy participants (scale, -4 to +4).

Table 4. Effect of High- and Low-Carbohydrate Diets on Body Weight and on Blood Lipid, Apolipoprotein, and C-Reactive Protein Concentrations (Intention-to-Treat Analysis)

Variable	High-Carbohydrate Control Diet			Low-Carbohydrate Test Diet			P Value ^a
	Week 0	Week 2	Week 4	Week 0	Week 2	Week 4	
Body weight, kg	86.6	83.9	82.3	82.4	80.1	78.5	.96
BMI	31.0	30.0	29.5	30.6	29.8	29.2	.91
Body fat, %	36.2	...	34.6	36.5	...	35.0	.95
HOMA-IR	1.7	1.1	1.0	1.5	0.9	1.0	.85
Satiety (-4 to 4)	1.1	0.9	0.8	1.3	1.6	1.4	.003
Cholesterol, mg/dL							
Total	254	221	222	257	202	205	.001
LDL-C	168	147	146	172	134	136	.002
HDL-C	50	46	47	48	46	46	.68
Triglycerides, mg/dL	187	138	147	189	113	113	.002
Ratios							
TC-HDL-C	5.37	4.92	4.94	5.64	4.63	4.64	.03
LDL-C-HDL-C	3.52	3.27	3.24	3.77	3.10	3.12	.02
Apolipoproteins							
apo AI, mg/dL	162	146	147	158	146	146	.71
apo B, mg/dL	137	118	118	139	108	108	.001
apo B-apo AI ratio	0.86	0.83	0.81	0.89	0.76	0.76	.003
hs-CRP, mg/L	2.13	1.22	1.44	2.70	1.87	1.81	.66

Abbreviations: apo AI, apolipoprotein AI; apo B, apolipoprotein B; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; ellipses, not measured.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert apolipoprotein to grams per liter, multiply by 0.01; to convert hs-CRP to nanomoles per liter, multiply by 9.524.

^aP values are based on intention-to-treat analysis, with baseline observation carried forward for subjects who did not complete the study, as assessed by the CONTRAST statement in SAS (using all available data) except for body weight and BMI, which were based on end values using general linear model with baseline carried forward.²⁴

LIPIDS

Both treatment groups had similar lipid values at baseline (Table 1). During the metabolic phase, reductions in LDL-C concentration and TC-HDL-C ratio were greater with the low-carbohydrate diet vs the high-carbohydrate diet (LDL-C: -20.4% [2.8%] vs -12.3% [2.6%] [$P=.002$]; and TC-HDL-C: -15.6% [3.4%] vs -6.8% [2.4%] [$P=.004$]). In addition, TC and TG concentrations were reduced with the low- vs the high-carbohydrate diet (TC: -19.8% [2.4%] vs -12.7% [2.2%] [$P=.001$]; and TG: -29.2% [5.5%] vs -17.8% [4.5%] [$P=.02$]). Similar patterns of significance were seen with the absolute lipid and lipoprotein concentrations (Table 4) and with the completers (Figure 3 and Figure 4). No treatment differences were seen for HDL-C.

APOLIPOPROTEINS

Apolipoprotein AI concentration fell for both treatment diets, and there was no difference between treatments ($P=.36$). However, both the apo B concentration and the apo B-apo AI ratio fell significantly more for the low-carbohydrate vs the high-carbohydrate diet by -21.1% (2.8%) vs -13.2% (2.2%) ($P=.001$) and -13.8% (3.4%) vs -4.2% (2.1%) ($P=.001$), respectively. A similar pattern was seen in completers (Figure 3).

hs-CRP, HbA_{1c}, BLOOD GLUCOSE, SERUM INSULIN AND INSULIN RESISTANCE, AND BP

No significant treatment differences in percentage change were seen in hs-CRP concentration ($P=.74$). Fasting blood

glucose, HbA_{1c}, and insulin concentrations and insulin resistance (calculated using homeostasis model assessment) fell similarly with both treatment diets during the course of the study (Table 4). Small but significantly greater reductions in systolic BP of -2.2 mm Hg (-1.9%; $P=.052$) and diastolic BP of -1.7 mm Hg (-2.4%; $P=.02$) were seen for the low-carbohydrate vs high-carbohydrate diet.

COMMENT

The present study demonstrated that consumption of a low-carbohydrate plant-based diet resulted in body weight reductions of 4 kg that were similar to those reported for low-carbohydrate Atkins-like diets.^{1,5-8} In addition to weight loss, the consumption of a low-carbohydrate diet containing vegetable proteins and oils was associated with significantly reduced concentrations of LDL-C, not reported in the majority of low-carbohydrate diet studies in which the protein and fat are largely of animal origin. These diets result in increases in LDL-C concentrations compared with routinely used higher carbohydrate therapeutic diets.^{5-8,25} The reduction in LDL-C concentration is a potentially important attribute of the diet in reducing CHD risk.^{26,27}

Our data support earlier conclusions that differences in weight loss between treatments are likely to result from a reduction in caloric intake rather than metabolic changes associated with an altered macronutrient profile,^{5,7,8,25} despite the possibility that high-protein low-carbohydrate diets might enhance postprandial thermogenesis.²⁸ In addition, the satiating effect of protein on self-selected diets, together with mild ketonemia following low-car-

bohydrate intake, might also favor weight reduction.²⁹ In the present study, carbohydrate intake on the low-carbohydrate diet met the minimum recommended level¹⁴; thus, significant ketonuria is unlikely, although it was not assessed.

Low-glycemic load diets have been associated with greater weight loss in adolescents.³⁰ Increased subjective ratings of satiety were also found for the low-carbohydrate test diet in the present study, which by virtue of being low in carbohydrates was also a low-glycemic load diet. A similar finding of increased satiety was found in a metabolically controlled study using a low-glycemic load weight-loss diet in younger adults.¹⁵

High-carbohydrate vegetarian diets such as the original Ornish diet, which emphasized soy and legume protein, have been associated with reduced progression of coronary artery disease, as well as weight loss and reduced LDL-C concentrations.³¹ However, such diets also lower HDL-C concentrations due to the impressively low intake of fats. Concern has been expressed over the use of high-carbohydrate diets, which may depress already low HDL-C concentrations further.³² The test diet in the present study, while lowering LDL-C concentration, did not depress HDL-C concentration significantly and resulted in a 16% reduction in the TC-HDL-C ratio. These changes would be expected to reduce CHD risk.^{26,27} Both soy and nuts, as key components of the present study, have been shown to increase HDL-C concentrations when included in low-fat diets.^{33,34}

Triglyceride concentrations were lower with consumption of the low-carbohydrate diet by comparison with the control diet, possibly reflecting the lower glycemic load and the presence of gluten, soy protein, and nuts, all of which have been associated with lower fasting serum TG concentrations.³⁵⁻³⁸

Most low-carbohydrate diets have not reported the effects on apolipoproteins. The reduction in apo B and the apo B-apo AI ratio observed in the present study is a further confirmation of the potential CHD benefit that might be expected from this dietary approach to body weight reduction.³⁹⁻⁴¹ In some studies, the apolipoprotein concentrations have been claimed to have greater predictive value for CHD events than more conventional lipid variables.⁴²

Both diets tended to reduce systolic and diastolic BP as expected relative to the degree to which body weight was reduced,⁴³ but with a greater BP reduction with the low-carbohydrate diet. High-protein diets have been associated with lower BP.⁴⁴ No treatment difference in hs-CRP concentration was seen in the present study, possibly related to the great variability in this measurement. In other studies, hs-CRP concentration tended to be lowest with the diets containing the highest proportion of carbohydrates,⁸ although low-glycemic index and low-glycemic load diets have also been associated with a lower hs-CRP concentration.^{45,46}

To our knowledge, no randomized controlled trials have been undertaken to assess the effect of low-carbohydrate diets on CHD events. Nevertheless, a recent cohort study reported that a low-carbohydrate diet high in protein and oil from vegetable rather than animal sources was associated with reduced CHD risk and

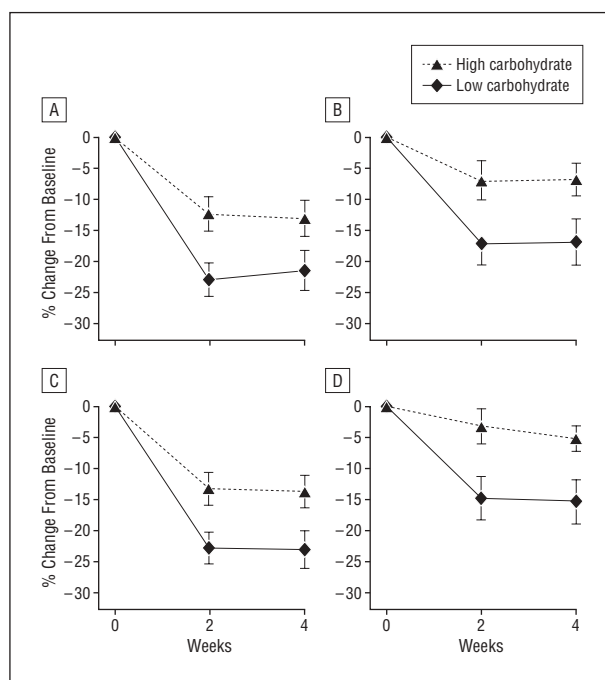


Figure 3. Mean (SE) percentage change from baseline in completers for both treatments for low-density lipoprotein cholesterol ($P=.001$) (A), total cholesterol-high-density lipoprotein cholesterol ratio ($P=.003$) (B), apolipoprotein B (apo B) ($P=.001$) (C), and apo B-apo AI ratio ($P=.001$) (D) (significance of difference between treatments).

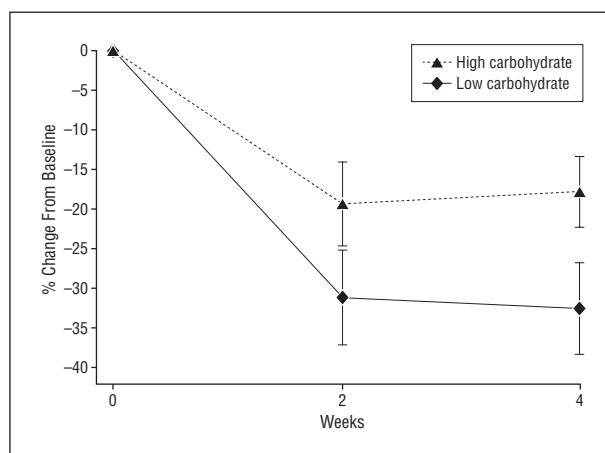


Figure 4. Mean (SE) percentage change from baseline in completers for both treatments for triglyceride concentration ($P=.02$) (significance of difference between treatments).

incidence of diabetes.^{47,48} The mean level with each decile of vegetable protein and oil in this cohort study was only 4.2% to 5.6% of energy for vegetable protein and 9.6% to 18.9% of energy for vegetable oil, considerably less than used in the present study.⁴⁷ Had the intakes been similar to the levels in the present study, the effects might have been greater.

In the present study, the high-carbohydrate control diet can be seen as providing a positive control because lacto-ovo vegetarians appear to be at generally lower risk of CHD than nonvegetarians, with notable studies demonstrating reduced CHD events in cohorts of California Seventh Day Adventists and the earlier assessment of British vegetarians.^{49,50} Furthermore, low-fat dairy diets em-

phasizing higher intakes of fruits and vegetables, such as the Dietary Approaches to Stop Hypertension (DASH) and Optimal Macro Nutrient Intake (OMNI) diets, have been associated with lower BP and improved serum lipid profiles.³ As such, the benefits for CHD risk reduction seen in the present study might have been much more marked had the low-carbohydrate diet been compared with those from a more typical low-fat diet.

According to the Mensink and Katan equation, the mean (SE) reductions in LDL-C concentration seen with the low-carbohydrate diet ($-37.07 [5.79]$ mg/dL) were greater than predicted ($-16.22 [1.16]$ mg/dL), even when adjusted for weight loss ($P < .001$).^{51,52} We believe that the greater than expected reductions in LDL-C concentrations are likely to be due in part to the cholesterol-lowering properties of soy protein and nuts, which have been demonstrated in previous studies.^{33,37,38,53,54} Furthermore, the small amount of carbohydrates included in the low-carbohydrate treatment diet was associated with viscous fiber in low-starch vegetables and β -glucan in oats and barley. Viscous fiber is also expected to contribute to the overall cholesterol-lowering effect of the diet.^{26,55,56} Vegetable protein has also been shown to be inversely related to BP in the cross-sectional epidemiological INTERMAP Study of 4680 individuals aged 40 to 59 from 4 countries.⁵⁷ Soy protein consumption has been associated with lower blood pressure in a number of feeding trials (ie, meta-analysis),⁵⁸ providing a further reason why vegetable proteins would be expected to reduce the risk of CHD.

In addition to reduction in LDL-C concentration, lower saturated fat intake may have other advantages, including reduced insulin resistance, chronic inflammation, and improved endothelial function,⁵⁹⁻⁶¹ all of which would contribute to the lower risk of CHD associated with reduced saturated fat intake.^{62,63} However, polyunsaturated fats⁶⁴ and vegetable oils in general^{47,63} in epidemiological studies have been shown to be associated with a reduced risk of CHD as opposed to saturated and *trans* fats, which are associated with increased risks. Key characteristics of a plant-based diet include fiber, vegetable oils and vegetable proteins, and foods such as nuts and seeds. These foods and food components benefit CHD risk factors, and it is therefore not surprising that plant-based diets have been associated with reduced CHD events in epidemiological studies.⁵⁰

We conclude that low-carbohydrate diets emphasizing vegetable sources of protein, such as gluten, soy, and nuts, together with vegetable oils can be used in weight reduction diets to improve serum lipid concentrations. There are, however, currently no trials of diets high in vegetable protein and oils with disease end points. The impact of low-carbohydrate diets in primary and secondary CHD prevention, therefore, remain to be determined. Nevertheless, recent studies indicate beneficial effects of vegetable oils and proteins on both CHD risk factors and CHD risk. Consumption of foods rich in these components including nuts and soy have been shown to reduce serum lipid concentrations, and nut consumption has been associated with lower CHD risk.⁶⁵

Important questions remain. Can the advantages be maintained if some of the vegetable protein is replaced by vegetable oil, and in this context, can carbohydrate

intake be further reduced or is there an optimal carbohydrate load, perhaps determined by an individual's BMI and insulin resistance.⁶⁶ There may also be certain advantages for higher carbohydrate intakes, providing the carbohydrate comes from high fiber, low-glycemic index foods. Pending answers to these questions, a plant-based low-carbohydrate diet high in vegetable proteins and oils may be an effective option in treating those with dyslipidemia for whom both weight loss and lower LDL-C concentrations are treatment goals.

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REFERENCES

- Shai I, Schwarzfuchs D, Henkin Y, et al; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med*. 2008;359(3):229-241.
- Appel LJ, Moore TJ, Obarzanek E, et al; DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336(16):1117-1124.
- Appel LJ, Sacks FM, Carey VJ, et al; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294(19):2455-2464.
- Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006;296(15):1885-1899.
- Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med*. 2003;348(21):2082-2090.
- Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA*. 2007;297(9):969-977.
- Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med*. 2003;348(21):2074-2081.
- Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA*. 2005;293(1):43-53.
- Sacks FM, Kass EH. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr*. 1988;48(3)(suppl):795-800.
- Jenkins DJ, Kendall CW, Marchie A, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290(4):502-510.
- Gardner CD, Coulston A, Chatterjee L, Rigby A, Spiller G, Farquhar JW. The effect of a plant-based diet on plasma lipids in hypercholesterolemic adults: a randomized trial. *Ann Intern Med*. 2005;142(9):725-733.
- US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. *Division of Nutrition and Physical Activity: Promoting Physical Activity: A Guide for Community Action*. Champaign, IL: Human Kinetics; 1999.
- Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25(1):71-80.
- Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington, DC: National Academies Press; 2005.
- Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA*. 2004;292(20):2482-2490.
- Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism in Man*. Washington, DC: Carnegie Institute of Washington; 1919. Publication 279.
- Shetty PS, Henry CJ, Black AE, Prentice AM. Energy requirements of adults: an update on basal metabolic rates (BMRs) and physical activity levels (PALs). *Eur J Clin Nutr*. 1996;50(suppl 1):S11-S23.
- Lipid Research Clinics Program. *Manual of Laboratory Operations: Lipid and Lipoprotein Analysis (Revised 1982)*. Washington, DC: US Government Printing Office, US Dept of Health and Human Services; 1982.
- Warnick GR, Benderson J, Albers JJ. Dextran sulfate-Mg²⁺ precipitation procedure for quantitation of high-density-lipoprotein cholesterol. *Clin Chem*. 1982;28(6):1379-1388.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.
- Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek E. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. *Clin Chem*. 2001;47(3):444-450.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
- US Department of Agriculture, Agricultural Research Service. USDA nutrient database for standard reference, release 19. Nutrient Data Laboratory Web site. Washington, DC: US Department of Agriculture, Agricultural Research Service; 2006. <http://www.ars.usda.gov/nutrientdata>. Accessed October 2005–July 2007.
- SAS Institute Inc. *SAS/STAT User's Guide (Version 6.12)*. Cary, NC: SAS Institute Inc; 2005.
- Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med*. 2004;140(10):778-785.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497.
- Grundey SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239.
- Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *J Am Coll Nutr*. 2004;23(5):373-385.
- St Jeor ST, Howard BV, Prewitt TE, Bovee V, Bazzarre T, Eckel RH; Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Dietary protein and weight reduction: a statement for health-care professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation*. 2001;104(15):1869-1874.
- Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP, Ludwig DS. A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med*. 2003;157(8):773-779.
- Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? the Lifestyle Heart Trial. *Lancet*. 1990;336(8708):129-133.
- Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu Rev Nutr*. 2005;25:391-406.
- Jenkins DJ, Kendall CW, Marchie A, et al. Dose response of almonds on coronary heart disease risk factors: blood lipids, oxidized low-density lipoproteins, lipoprotein(a), homocysteine, and pulmonary nitric oxide: a randomized, controlled, crossover trial. *Circulation*. 2002;106(11):1327-1332.
- Jenkins DJ, Kendall CW, Jackson CJ, et al. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *Am J Clin Nutr*. 2002;76(2):365-372.
- Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr*. 2001;73(3):560-566.

36. Jenkins DJ, Kendall CW, Vidgen E, et al. High-protein diets in hyperlipidemia: effect of wheat gluten on serum lipids, uric acid, and renal function. *Am J Clin Nutr.* 2001;74(1):57-63.
37. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med.* 1995;333(5):276-282.
38. Sabaté J, Fraser GE, Burke K, Knutsen SF, Bennett H, Lindsted KD. Effects of walnuts on serum lipid levels and blood pressure in normal men. *N Engl J Med.* 1993;328(9):603-607.
39. Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation.* 2000;101(5):477-484.
40. Sniderman AD, Furberg CD, Keech A, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet.* 2003;361(9359):777-780.
41. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.
42. McQueen MJ, Hawken S, Wang X, et al; INTERHEART Study Investigators. Lipids, lipoproteins, and apolipoproteins as risk factors of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet.* 2008;372(9634):224-233.
43. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension.* 2003;42(5):878-884.
44. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA. Relationship to blood pressure of combinations of dietary macronutrients: findings of the multiple risk factor intervention trial (MRFIT). *Circulation.* 1996;94(10):2417-2423.
45. Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am J Clin Nutr.* 2002;75(3):492-498.
46. Wolever TM, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycosylated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr.* 2008;87(1):114-125.
47. Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006;355(19):1991-2002.
48. Halton TL, Liu S, Manson JE, Hu FB. Low-carbohydrate-diet score and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2008;87(2):339-346.
49. Appleby PN, Thorogood M, Mann JI, Key TJ. The Oxford Vegetarian Study: an overview. *Am J Clin Nutr.* 1999;70(3)(suppl):525S-531S.
50. Fraser GE. *Diet, Life Expectancy, and Chronic Disease: Studies of Seventh-Day Adventists and Other Vegetarians.* New York, NY: Oxford University Press; 2003.
51. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr.* 2003;77(5):1146-1155.
52. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr.* 1992;56(2):320-328.
53. Sirtori CR, Agradi E, Conti F, Mantero O, Gatti E. Soybean-protein diet in the treatment of type-II hyperlipoproteinaemia. *Lancet.* 1977;1(8006):275-277.
54. Kris-Etherton PM, Yu-Poth S, Sabate J, Ratcliffe HE, Zhao G, Etherton TD. Nuts and their bioactive constituents: effects on serum lipids and other factors that affect disease risk. *Am J Clin Nutr.* 1999;70(3)(suppl):504S-511S.
55. Jenkins DJ, Newton C, Leeds AR, Cummings JH. Effect of pectin, guar gum, and wheat fibre on serum-cholesterol. *Lancet.* 1975;1(7916):1116-1117.
56. Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr.* 2004;23(1):5-17.
57. Elliott P, Stamler J, Dyer AR, et al. Association between protein intake and blood pressure: the INTERMAP Study. *Arch Intern Med.* 2006;166(1):79-87.
58. He J, Gu D, Wu X, Chen J, Whelton PK. Effect of soybean protein on blood pressure: a randomized, controlled trial. *Ann Intern Med.* 2005;143(1):1-9.
59. Ferrannini E, Barrett EJ, Bevilacqua S, DeFronzo RA. Effect of fatty acids on glucose production and utilization in man. *J Clin Invest.* 1983;72(5):1737-1747.
60. Keogh JB, Grieger JA, Noakes M, Clifton PM. Flow-mediated dilatation is impaired by a high-saturated fat diet but not by a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol.* 2005;25(6):1274-1279.
61. Kennedy A, Martinez K, Chuang CC, LaPoint K, McIntosh M. Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. *J Nutr.* 2009;139(1):1-4.
62. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: the Ireland-Boston Diet-Heart Study. *N Engl J Med.* 1985;312(13):811-818.
63. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med.* 1997;337(21):1491-1499.
64. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. *Am J Epidemiol.* 2005;161(7):672-679.
65. Hu FB, Stampfer MJ, Manson JE, et al. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *BMJ.* 1998;317(7169):1341-1345.
66. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000;71(6):1455-1461.