Effect of a Very–High-Fiber Vegetable, Fruit, and Nut Diet on Serum Lipids and Colonic Function

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We tested the effects of feeding a diet very high in fiber from fruit and vegetables. The levels fed were those, which had originally inspired the dietary fiber hypothesis related to colon cancer and heart disease prevention and also may have been eaten early in human evolution. Ten healthy volunteers each took 3 metabolic diets of 2 weeks duration. The diets were: high-vegetable, fruit, and nut (very–high-fiber, 55 g/1,000 kcal); starch-based containing cereals and legumes (early agricultural diet); or low-fat (contemporary therapeutic diet). All diets were intended to be weight-maintaining (mean intake, 2,577 kcal/d). Compared with the starch-based and low-fat diets, the high-fiber vegetable diet resulted in the largest reduction in low-density lipoprotein (LDL) cholesterol (33% ± 4%, $P < .001$) and the greatest fecal bile acid output (1.13 ± 0.30 g/d, $P = .002$), fecal bulk (906 ± 130 g/d, $P < .001$), and fecal short-chain fatty acid outputs (78 ± 13 mmol/d, $P < .001$). Nevertheless, due to the increase in fecal bulk, the actual concentrations of fecal bile acids were lowest on the vegetable diet (1.2 mg/g wet weight, $P = .002$). Maximum lipid reductions occurred within 1 week. Urinary mevalonic acid excretion increased ($P = .036$) on the high- vegetable diet reflecting large fecal steroid losses. We conclude that very high-vegetable fiber intakes reduce risk factors for cardiovascular disease and possibly colon cancer. Vegetable and fruit fibers therefore warrant further detailed investigation.

EARLY DISCUSSIONS OF the health benefits of dietary fiber focused on cereal fibers, especially wheat bran, and attributed many western diseases including colon cancer, heart disease, and diabetes to changes in milling practices in the 19th century.[1] These changes had resulted in large-scale production of white flour and loss of cereal fiber from the diet. It was suggested that a return to high-fiber diets may prevent a range of health problems.[2] Wheat fiber is now well recognized as an effective bulk laxative in the treatment of constipation of dietary origin. Studies have also repeatedly shown the advantages of cereal fiber in reducing risk of heart disease and diabetes,[3-9] especially in the context of low glycemic index diets[8-10] and milled whole grain cereal foods.[11] However, the predicted action of cereal fiber in preventing colonic disease, notably colon cancer, has not been supported by recent cohort studies of colon cancer[12] or polyp prevention trials using wheat bran.[13]

Nevertheless, the diets and disease patterns of sub-Sahara Africa, and Uganda in particular, provided the original impetus for the dietary fiber hypothesis of Burkitt and Trowell[14] and rekindled interest in fiber in the early 1970s. These African diets were very high in vegetable fiber, maize, and millet, while wheat fiber was notably absent. Yet despite the origins of the fiber hypothesis, for western societies the term fiber has become synonymous with wheat bran. At the same time, the evolutionary aspect of the hypothesis has continued to provide support for the concept that humans are adapted to high-fiber intakes, but in this case, the focus of interest has remained vegetables and fruit.[15-18] Significant cereal consumption is considered to have occurred relatively recently with the agricultural revolution 8 to 10 thousand years ago and therefore with very little impact on the human genome. Nevertheless, comparatively little attention has been paid to fruit and vegetable fibers,[19] and even fewer studies have tested the effect of feeding whole foods.[20] In studies undertaken on vegetables and fruit, the results in terms of colonic disease, have not shown anticipated benefits.[21] However, although the current goals for fiber intake were met, the amount of fiber consumed was far below that seen in tropical Africa or suggested to have been eaten earlier during the course of human evolution.

We have therefore assessed the effects on serum lipids, fecal bulk, bile acids, and short-chain fatty acids (SCFA) of very–high-fiber diets. Serum lipids were measured as markers for cardiovascular disease risk.[22] Fecal bile acid losses were analyzed both to assess the mechanism by which serum cholesterol levels might be lowered by fiber[23] and because reductions in fecal bile acid concentrations have been associated with a reduced risk of colon cancer.[24] Similarly, fecal short-chain fatty acids were determined because increased butyrate resulting from fiber fermentation in the colon has been considered to have antineoplastic properties and to be an important energy source in maintaining a healthy colonic mucosa.[25,26] Of these diets studied, 1 diet was very high in fiber from vegetables and

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fruit, and the other was a high-starch diet based on unrefined cereals and legumes. These 2 diets were compared with the third diet, which was a contemporary low saturated fat therapeutic diet as used in the treatment of hyperlipidemia.[22] The first diet also represented a possible model for the mix of fiber sources consumed earlier in human evolution and still eaten in parts of tropical Africa, while the second can be seen as representing an early agricultural diet containing many of the elements of the contemporary Mediterranean diet.

MATERIALS AND METHODS

We studied 10 healthy subjects (8 men, 2 women) with a mean (± SEM) age of 38 ± 4 years (range, 24 to 60) and a body mass index of 25 ± 1 kg per m^2 (range, 21 to 32) recruited from hospital and university staff and graduate students who were prepared to eat large amounts of leafy vegetables. Three subjects were lactovegetarians. None were taking medications with the exception of 1 subject who was hypothyroid and on long-term thyroxine. He continued to take 0.2 mg/d L-thyroxine over the entire study period. None had biochemical or clinical evidence of diabetes, renal, or hepatic disease. Subjects were asked to maintain the same level of physical activity during all 3 study periods.

All subjects undertook three 2-week metabolic diets: high-vegetable, high-starch, and low–saturated-fat (therapeutic diet).[22] The vegetable and starch diets were taken in a randomized crossover design in the first 2 phases (5 subjects ate the vegetable-based diet first and the starch-based diet in the second phase, while the other 5 took the diets in the reverse order). The low-fat diet was taken in a third phase, because after randomization for the first phase, it was realized that the vegetable-based diet should also be compared with a contemporary therapeutic diet. The average time interval was 9.2 ± 0.3 months between the first and second phases and 8.9 ± 0.2 months between the second and third phases, such that food availability was similar on both occasions when the vegetable-based diet was provided. Fasting blood and body weights were obtained at the beginning and end of each study period with additional blood samples obtained on day 7 of phases 2 and 3. Twenty-four–hour urine and 3-day fecal collections were obtained at the end of each period. Collections were made on an outpatient basis at the end of each metabolic diet. Patients were provided with underseat lavatory frames on which to attach plastic collection bags. After use, bags were sealed, labeled, and placed on dry ice in a polystyrene container. At the end of 3 days, these containers were returned by courier to the laboratory where samples were weighed and stored at −20°C. Pooled 3-day collections were then partially thawed, placed in a 5-L capacity blender with addition of 10% water by weight, and homogenized. Aliquots of 300 g were then freeze-dried, weighed, and stored at -20°C before being analyzed.

Diets

Subjects followed a 3-day rotating menu on the high-fiber vegetable-based diet, which consisted of leafy and low-calorie vegetables with an emphasis on leafy vegetables and pods, fruits, and nuts, but without starch-containing foods, including cereals, dried legumes, or root vegetables. This very high intake of fruit and vegetables translated into 63 servings per day for a 2,500 kcal diet (Table 1). The other 2 diets used 1-day repeating menu. For the starch-based diet, these consisted of whole grain cereals, legumes, low-fat dairy products, olives, and olive oil and 11 servings per day of fresh fruit and vegetables (Table 1). The low-fat therapeutic diet foods included low-fiber starchy foods, skim milk dairy products, olive, and safflower oils, together with 5 servings per day of fruit (Table 1). Subjects were provided with all food to be eaten in preweighed amounts at twice weekly intervals. During each phase, subjects recorded their feelings of hunger on a bipolar semantic scale in which –3 was very hungry and +3 was very satiated.

Composite 1-day diets were prepared from each of the 3 phases and analyzed for macronutrients[27] and dietary fiber[28] by Association of Official Analytical Chemists methods (Table 2). Fatty acids, cholesterol, and plant sterols were determined by gas liquid chromatography (Table 2).[29] The analyzed values were within reasonable agreement with calculated values. For the 3 diets, the mean analyzed values expressed as a percentage of the calculated values were 108.2% protein, 100.2% fat, and 98.6% available carbohydrate. The higher protein value was due to the higher than expected protein content of the vegetable-based diet. The daily caloric intake for the 3 days of the vegetable-based diet, starch-based diet, and low-fat therapeutic diet, expressed as a percentage of their respective calculated values using a modified US Department of Agriculture (USDA) database[30] were: 99.6%, 100.4%, 96.0%, 108.3%, and 97.2%. These values were used to adjust the mean calculated caloric intake for each diet (Table 2).

Analyses

Serum stored at −70°C was analyzed for total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol after dextran sulphate magnesium chloride precipitation by techniques of the Lipids Research Clinics.[31] Low-density lipoprotein (LDL) cholesterol was calculated.[32] Serum apoplipoprotein A-I and B were measured by a nephelometric technique[33] and lipoprotein(a) [Lp(a)] was measured with a commercial enzyme-linked immunosorbent assay (Macra Lp[a]; Trinity Biotech, Jamestown, NY).

Aliquots of 24-hour urine collections, stored at −70°C were also analyzed for mevalonate[34] and C-peptide.[35] Short-chain fatty acids were determined in feces by high-pressure liquid chromatography[36] after vacuum distillation[37] of thawed feces, which had previously been stored at −70°C. Concentrations were expressed as mmol/L assuming 1 kg of feces was equivalent to 1 L. Daily output was derived by multiplying the fecal weight in kilograms by the concentration. Fecal bile acids were determined in finely ground freeze-dried feces by gas-liquid chromatography with a DB-I column (J&W Scientific, Folson, CA), and 5β-cholanic acid as an internal standard.[38] Bile acid concentration was calculated as milligram bile acid per gram freeze-dried feces and expressed in the Results as milligrams per gram fecal wet weight. Bile acid output was derived from multiplying the concentration by the mean daily fecal weight. The chenodeoxycholate acid synthesis rate was calculated from the sum of the bile acids excreted in the feces per day that lacked a C-12 hydroxyl group.[39,40] Cholic acid synthesis rate was calculated from the sum of all bile acids that had a C-12 hydroxyl group.[39,40] These calculations assume a steady state.[39,40]

Plant sterols and cholesterol were measured by high-pressure liquid chromatography[41] on freeze-dried feces and freeze-dried 24-hour composites of the 7-day test and control diets.

Statistics

The results are expressed as means ± SEM. The percentage changes across each of the 3 diets for week 2 values were expressed as percentage of their respective pretreatment values. The significance of these changes was assessed by Student's *t* test for paired data (2-tailed). The treatment effect was expressed as the change from baseline. Absolute and percentage differences between treatments were assessed using the Student-Newman-Keuls procedure in SAS[42] after establishing a significant F-value by analysis of variance. Treatment and sex were categorical variables, and the baseline value for each phase was a covariate. The same model was used for the CONTRAST statement in PROC GLM/SAS to assess the difference between the vegetable-based diet and the other 2 diets.[42]

Table 1. Repeating Menus as Eaten on the Therapeutic and Starch Diets and the 3-Day Repeating Menu Eaten on the Vegetable Diet

Therapeutic Diet	Starch Diet	Vegetable Diet—Day 1	Vegetable Diet—Day 2	Vegetable Diet—Day 3
Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
205 g orange juice	65 g oats	32 g filberts	202 g avocado	33 g almonds
72 g cream of wheat	43 g dates	302 g raspberries	184 g fresh figs	302 g blueberries
22 g safflower oil	26 g dried figs	302 g honeydew melon	332 g raspberries	333 g mango
26 g brown sugar	177 g yogurt	302 g banana	302 g banana	301 g banana
129 g skim milk	44 g raisins			
78 g banana	117 g banana			
154 g yogurt				
23 g jam				
Lunch	Lunch	Lunch	Lunch	Lunch
159 g fat-free cheese	104 g whole wheat bread	503 g Brussels sprouts	302 g okra	100 g okra
96 g white bread	163 g 1% cottage cheese	302 g okra	256 g green peas	252 g green peas
153 g yogurt	127 g tomato	302 g green peas	302 g snow peas	302 g red pepper
23 g jam	172 g pears	322 g mushrooms	503 g cabbage	302 g snow peas
281 g apple with skin	147 g apple	32 g filberts	231 g onion	503 g cabbage
		322 g plum	704 g tangerine	33 g almonds
			302 g apple	322 g grapes
Dinner	Dinner	Dinner	Dinner	Dinner
Cheese omelette	Bean casserole	503 g broccoli	302 g asparagus	503 g broccoli
103 g Lipton's Egg Beaters (egg substitute)	31 g chickpeas	302 g eggplant	503 g broccoli	302 g eggplant
	41 g lentils	302 g carrots	302 g eggplant	302 g carrot
159 g fat free cheese	104 g brown rice	252 g snow peas	302 g carrots	302 g tomato
46 g olive oil*	65 g olives	32 g filberts	353 g honeydew melon	201 g onion
42 g mashed potato flakes	64 g 7% mozzarella cheese	302 g strawberries		33 g almonds
61 g white rice		604 g tangerines		302 g pears
58 g broccoli	38 g olive oil			100 g kiwi fruit
132 g pears	129 g broccoli			
	118 g banana			

NOTE. Water, black tea, and coffee allowed ad libitum.

*Olive oil used for omelette preparation and also with instant mashed potato and boiled rice.

Table 2. Dietary Profile of Macronutrients, Fatty Acids, Fiber, and Sterols as Analyzed on 24-Hour Dietary Composites

	Low-Fat Therapeutic	Starch	Vegetable
Energy (kcal per day)*	2,509	2,415	2,706
Total protein (percent of energy)	19.2	15.0	18.2
Total fat (percent of energy)	23.9	21.4	22.2
SFA (percent of energy)	3.7	4.1	2.7
MUFA (percent of energy)	12.9	8.8	12.2
PUFA (percent of energy)	7.9	5.8	5.3
PUFA to SFA ratio	2.1	1.4	2.0
Available carbohydrate (percent of energy)	56.9	63.4	59.6
Total dietary fiber (g per 1,000 kcal)	10.0	18.8	55.3
Dietary cholesterol (mg per 1,000 kcal)	17	8	0†
Phytosterols (mg per 1,000 kcal)			
Campesterol (mg per 1,000 kcal)	12	18	52
Stigmasterol (mg per 1,000 kcal)	2	6	22
Sitosterol (mg per 1,000 kcal)	87	145	313

Abbreviations: SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

*Mean energy intake of subjects calculated using the dietary database and adjusted according to analytical values from the 1-day diet composites.

†A total of 1.9 mg/d as analyzed, but assumed cholesterol was 0, because no animal products were consumed on this diet.

RESULTS

Compliance with the 3 diets was adequate with 96.5% ± 1.3% of prescribed calories consumed. On the high-fiber vegetable-based diet, the men consumed 94.1% ± 3.6%, while the women consumed 89.5% ± 4.5%. On all diets, subjects tended to lose weight: vegetable-based, 0.4 ± 0.3 kg ($P = .240$); starch-based, 0.1 ± 0.2 kg ($P = .675$); and low-fat therapeutic diet, 0.6 ± 0.4 kg ($P = .133$). With the maximum satiety rating as 3.0, satiety ratings were highest on the vegetable-based diet (3.0 ± 0.0) compared with the starch-based (1.9 ± 0.5) and low-fat diets (0.7 ± 0.5) and related to the daily weight of food consumed (vegetable-based, 5.1 ± 0.3 kg/d; range, 3.6 to 6.3 kg/d; starch-based, 1.9 ± 0.9 kg/d; range, 1.5 to 2.4 kg/d; and low-fat therapeutic diet, 2.0 ± 0.1 kg/d; range, 1.4 to 2.4 kg/d) ($r = .57$, $P = .001$).

Serum Lipids and Blood Pressure

The greatest percentage reductions in blood lipids and lipoproteins were seen on the high-fiber vegetable-based diet (Tables 3 and 4), followed by the starch-based diet, while no significant change was seen on the therapeutic diet. There were no significant differences in the week 0 values between treatments. The 3 vegetarians showed similar responses to the other

Table 3. Body Weight, Serum, and Blood Pressure Data for the Metabolic Periods (mean ± SE) (n = 10)

	Therapeutic Diet		Starch Diet		Vegetable Diet		
	Week 0*	Week 2	Week 0*	Week 2	Week 0*	Week 2	P†
Body weight (kg)	75.7 ± 3.5	75.1 ± 3.6[a]	76.3 ± 4.0	76.2 ± 4.0[b]	77.0 ± 4.8	76.6 ± 4.9[b]	.936
Cholesterol							
Total-C (mmol/L)	4.70 ± 0.22	4.44 ± 0.22[a]	4.79 ± 0.26	3.87 ± 0.19[b]	4.72 ± 0.29	3.67 ± 0.27[b]	.007
LDL-C (mmol/L)	2.92 ± 0.23	2.73 ± 0.24[a]	2.96 ± 0.26	2.25 ± 0.17[b]	2.99 ± 0.32	2.01 ± 0.25[c]	<.001
HDL-C (mmol/L)	1.17 ± 0.10	1.15 ± 0.09[a]	1.14 ± 0.07	1.02 ± 0.10[b]	1.09 ± 0.08	0.98 ± 0.07[b]	.223
Triglycerides (mmol/L)	1.54 ± 0.31	1.38 ± 0.26[a]	1.70 ± 0.40	1.34 ± 0.22[a]	1.76 ± 0.56	1.64 ± 0.47[a]	.381
Apolipoproteins							
Apo A-I (g/L)	1.45 ± 0.07	1.42 ± 0.08[a]	1.52 ± 0.06	1.32 ± 0.08[a]	1.45 ± 0.05	1.33 ± 0.06[a]	.855
Apo B (g/L)	1.14 ± 0.08	1.07 ± 0.08[a]	1.13 ± 0.08	0.90 ± 0.05[b]	1.18 ± 0.11	0.87 ± 0.08[b]	.002
Lp(a) (mg/L)	11.1 ± 2.4	13.9 ± 2.5	10.2 ± 2.3	11.8 ± 2.7[a]	10.3 ± 2.0	9.7 ± 1.4[a]	.093
Ratios							
Total-C:HDL-C	4.32 ± 0.45	4.08 ± 0.36[a]	4.35 ± 0.35	4.07 ± 0.38[a]	4.58 ± 0.50	4.01 ± 0.53[a]	.156
LDL-C:HDL-C	2.61 ± 0.30	2.49 ± 0.31[a]	2.60 ± 0.26	2.28 ± 0.28[b]	2.69 ± 0.31	2.01 ± 0.27[c]	<.001
Apo B:Apo A-I	0.80 ± 0.07	0.77 ± 0.08[a]	0.76 ± 0.06	0.71 ± 0.06[b]	0.82 ± 0.08	0.66 ± 0.07[b]	<.001
Blood pressure (mm Hg)							
Systolic	125 ± 6	117 ± 4[a]	124 ± 6	120 ± 4[a]	123 ± 6	120 ± 5[a]	.215
Diastolic	77 ± 2	77 ± 2[a]	80 ± 2	74 ± 2[a]	80 ± 3	77 ± 2[a]	.742

NOTE. To convert cholesterol and triglycerides to mg/dL, multiply by 38.67 and 88.57, respectively. To convert apolipoprotein A-I and B values to mg/dL, multiply by 10.

*Baseline values were not significantly different between treatments.

†*P* value for the comparison of the mean of the week 2 therapeutic and starch diets *v* the vegetable diet using the CONTRAST statement in SAS.

[a,b,c]Different superscript letters represent significant differences between treatments ($P < .05$) in the same measurement at week 2 (Student-Newman-Keuls in SAS.

subjects. On the vegetable-based diet, reductions were seen in total cholesterol (22% ± 3%, $P < .001$), LDL cholesterol (33% ± 4%, $P < .001$), and the ratios of total to HDL cholesterol (13% ± 3%, $P = .003$), LDL to HDL cholesterol (24% ± 4%, $P < .001$) and apolipoprotein B to AI (19% ± 3%, $P < .001$) (Fig 1). On the starch-based diet, the serum lipids and lipoproteins were significantly reduced, but the reductions were of smaller magnitude than the vegetable-based diet and the reductions in the total:HDL cholesterol, LDL:HDL cholesterol, and apolipoprotein B:AI ratios did not reach significance (Fig 1).

Table 4. Absolute Changes in Body Weight, Serum, and Blood Pressure Data Between Week 0 and Week 2 on the Three Treatments (mean ± SE) (n = 10)

	Therapeutic Diet		Starch Diet		Vegetable Diet	
	Change	P	Change	P	Change	P
Body weight (kg)	−0.58 ± 0.35[a]	.133	−0.10 ± 0.23[a]	.675	−0.38 ± 0.30[a]	.240
Cholesterol						
Total-C (mmol/L)	−0.26 ± 0.12[a]	.056	−0.92 ± 0.14[b]	.000	−1.05 ± 0.14[b]	.000
LDL-C (mmol/L)	−0.19 ± 0.09[a]	.086	−0.71 ± 0.16[b]	.002	−0.98 ± 0.14[b]	.000
HDL-C (mmol/L)	−0.02 ± 0.03[a]	.493	−0.12 ± 0.04[a]	.023	−0.11 ± 0.03[a]	.007
Triglycerides (mmol/L)	−0.16 ± 0.22[a]	.498	−0.35 ± 0.29[a]	.256	−0.12 ± 0.12[a]	.360
Apolipoproteins						
Apo A-I (g/L)	−0.03 ± 0.04[a]	.400	−0.20 ± 0.03[b]	.000	−0.12 ± 0.04[ab]	.022
Apo B (g/L)	−0.07 ± 0.04[a]	.073	−0.23 ± 0.05[b]	.001	−0.31 ± 0.05[b]	.000
Lp(a) (mg/L)	2.83 ± 0.91[a]	.012	1.62 ± 1.79[a]	.390	−0.60 ± 1.42[a]	.683
Ratios						
Total-C:HDL-C	−0.24 ± 0.17[a]	.195	−0.28 ± 0.17[a]	.140	−0.57 ± 0.15[a]	.005
LDL-C:HDL-C	−0.12 ± 0.08[a]	.203	−0.32 ± 0.17[a]	.104	−0.68 ± 0.13[b]	.001
Apo B:Apo A-I	−0.03 ± 0.03[a]	.395	−0.05 ± 0.03[a]	.196	−0.16 ± 0.03[b]	.001
Blood pressure (mm Hg)						
Systolic	−8.65 ± 3.05[a]	.020	−4.62 ± 3.00[a]	.158	−3.20 ± 2.77[a]	.277
Diastolic	0.15 ± 2.72[a]	.957	−5.93 ± 2.12[a]	.021	−3.05 ± 1.59[a]	.087

NOTE. To convert cholesterol and triglycerides to mg/dL, multiply by 38.67 and 88.57, respectively. To convert apolipoprotein A-I and B values to mg/dL, multiply by 10.

[a,b,c]Different superscript letters represent significant differences ($P < .05$) in absolute changes between treatments for the same measurement (Student Newman Keuls in SAS).

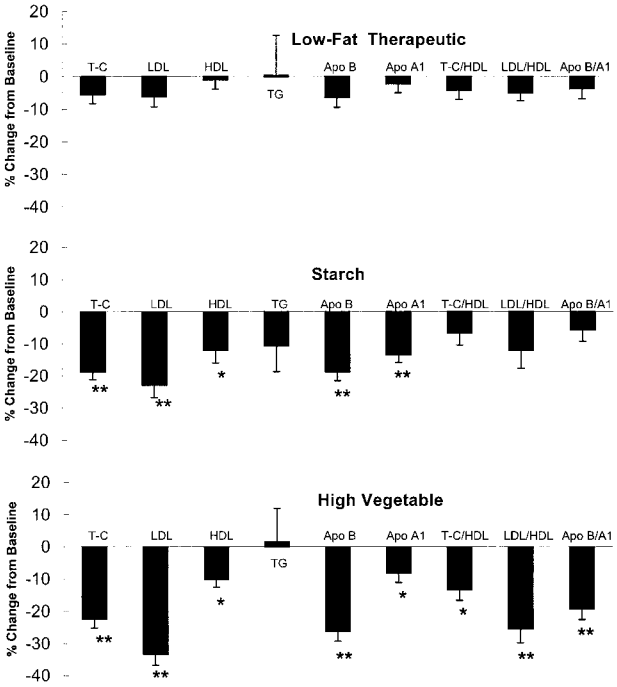

Fig 1. Percent change (mean [± SEM]) from baseline in serum lipoprotein and apolipoprotein concentrations after 2 weeks on the low-fat, starch-based, and vegetable-based diets (n = 10). (* *P* < .05; ** *P* < .001; represent significant within treatment changes, assessed by Student's *t* test for paired data, 2-tailed in SAS[42]).

None of the reductions in lipids, lipoproteins, or their ratios reached significance on the low-fat therapeutic diet (Fig 1). Comparison of the lipid reductions on these diets by the Student-Newman-Keuls procedure indicated that both the high-fiber vegetables and the starch diet showed significantly greater reductions ($P < .01$) than the respective low-fat therapeutic diet values for total cholesterol (22% ± 3% and 19% ± 2% *v* 6% ± 3%), LDL cholesterol (33% ± 4% and 23% ± 4% *v* 7% ± 3%) and apolipoprotein B (26% ± 3% and 19% ± 3% *v* 6% ± 3%) (Fig 1). Moreover, reductions were greatest ($P < .01$) on the high-fiber vegetable diet compared with both the starch and therapeutic diets for the LDL:HDL cholesterol ratio (24% ± 4% *v* 12% ± 6% and 5% ± 3%) and the apolipoprotein B:AI ratio (19% ± 3% *v* 6% ± 4% and 4% ± 3%) (Fig 1). The significance of the differences was confirmed using the CONTRAST determination ($P < .001$) (Table 3). The findings for the percentage change data were confirmed using the absolute 0 to 2-week differences (Table 4). The relatively rapid time course of the lipid reductions is shown in Fig 2 with near maximal reductions achieved after 1 week. No treatment difference was seen in blood pressure.

Urinary Mevalonate and C-Peptide

Twenty-four-hour urine volume and C-peptide were not different between treatments, but a significantly higher urinary mevalonate output was seen on the high-fiber vegetable-based diet (3.15 ± 0.17 μmol/d, $P = .036$) compared with the other 2 treatments (therapeutic diet, 2.27 ± 0.17 μmol/d; and starch-based diet, 2.75 ± 0.34 μmol/d) indicating increased cholesterol biosynthesis to replenish increased sterol (bile acid) losses (Table 5).

Fecal Bulk, Bile Acids, Cholesterol, and Short-Chain Fatty Acids

The high-fiber vegetable-based diet significantly increased daily fecal weight, expressed both as wet and dry weight, and increased fecal water content (Table 5). For the men, the mean fecal wet weight on the high-fiber vegetable-based diet exceeded 1 kg per day (1.0 ± 0.1 kg/d). Total fecal bile acid

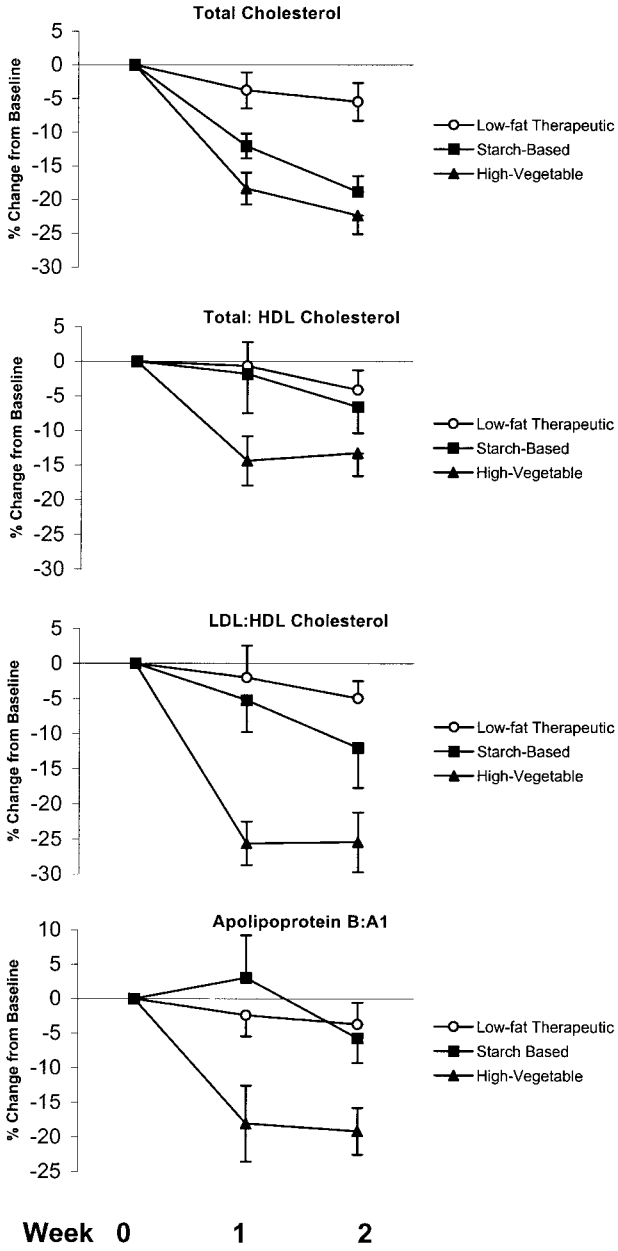

Fig 2. Serum cholesterol and lipoprotein and apolipoprotein ratio percent changes after 1 and 2 weeks on the low-fat, starch-based, and vegetable-based diets.

Table 5. Urinary and Fecal Output Data on and Test Metabolic Diets (mean ± SE) (n = 10)

	Therapeutic Diet	Starch Diet	Vegetable Diet	*P**
Urinary Data				
Daily output (L/d)	2.53 ± 0.34	3.13 ± 0.40	3.16 ± 0.30	.159
C-peptide (nmol/d)	0.02 ± 0.01	0.02 ± 0.00	0.03 ± 0.01	.163
Mevalonate (umol/d)	2.27 ± 0.17	2.75 ± 0.34	3.15 ± 0.17	.036
Fecal Data				
Fecal output (g/d)				
Wet wt	172 ± 28	279 ± 27	906 ± 130	.000
Dry wt	42 ± 7	68 ± 5	160 ± 24	.000
Fecal pH	6.85 ± 0.09	6.48 ± 0.09	6.55 ± 0.14	.298
Cholesterol output (mg/d)	451 ± 99	430 ± 91	850 ± 218	.002
Bile acid outputs (mg/d)				
Total bile acids	653 ± 172	508 ± 112	1,126 ± 299	.002
Cholate	125 ± 66	41 ± 25	198 ± 73	.063
Chenodeoxycholate	56 ± 21	27 ± 19	65 ± 27	.218
Deoxycholate	259 ± 50	222 ± 37	421 ± 94	.010
Lithocholate	192 ± 54	208 ± 59	429 ± 176	.028
Ursodeoxycholate	21 ± 8	10 ± 7	12 ± 6	.631
Primary bile acids	202 ± 90	78 ± 45	275 ± 99	.078
Secondary bile acids	451 ± 99	430 ± 91	850 ± 218	.002
Secondary:primary bile acids	8.6 ± 2.6	15.8 ± 8.4	3.6 ± 0.7	.239
Bile acid synthesis rates (mg/d)				
Cholate synthesis	384 ± 100	262 ± 45	619 ± 130	.001
Chenodeoxycholate synthesis	269 ± 74	246 ± 76	506 ± 199	.025
Total bile acid concentration (mg/g wet wt)	4.0 ± 1.0	2.0 ± 0.6	1.2 ± 0.2	.002
Short-chain fatty acid outputs (mmol/d)				
Formate	0.6 ± 0.1	0.8 ± 0.1	2.7 ± 0.3	.000
Acetate	8.4 ± 1.7	17.7 ± 2.8	52.3 ± 9.0	.000
Propionate	2.5 ± 0.6	3.7 ± 0.4	8.7 ± 2.4	.003
Butyrate	2.3 ± 0.5	5.5 ± 1.1	12.7 ± 2.3	.000
Valerate	0.3 ± 0.1	0.2 ± 0.0	0.4 ± 0.2	.389
Total SCFA	14.7 ± 3.0	28.5 ± 3.8	77.8 ± 13.3	.000
Short-chain fatty acid concentrations (mmol/L)				
Acetate	51.9 ± 6.8	65.3 ± 6.5	58.9 ± 4.0	.966
Propionate	14.7 ± 2.8	14.1 ± 1.5	9.2 ± 1.3	.015
Butyrate	13.6 ± 2.4	20.2 ± 3.0	14.2 ± 0.9	.290
Short-chain fatty acid molar ratios				
Acetate:total SCFA	0.58 ± 0.02	0.61 ± 0.03	0.67 ± 0.02	.003
Propionate:total SCFA	0.15 ± 0.01	0.14 ± 0.02	0.11 ± 0.02	.009
Butyrate:total SCFA	0.15 ± 0.01	0.19 ± 0.02	0.16 ± 0.01	.760
Propionate:acetate	0.27 ± 0.03	0.24 ± 0.04	0.16 ± 0.03	.003

*P value for comparison of the mean of the therapeutic and starch diets to the vegetable diet using the CONTRAST statement in SAS.[42]

output was higher on the vegetable-based diet (1.13 ± 0.30 g/d, $P = .002$) compared with the other 2 treatments (therapeutic diet, 0.65 ± 0.17 g/d; and starched-based diet, 0.51 ± 0.11 g/d), and the same was true for fecal cholesterol excretion (0.85 ± 0.22 g/d *v* 0.45 ± 0.10 g/d and 0.43 ± 0.09 g/d, respectively, $P = .002$) (Table 5). However, due to the higher fecal bulk, fecal bile acid concentrations were lowest on the high-fiber vegetable-based diet ($P = .003$) (Table 5). Fecal propionate concentration and the ratio of propionate to acetate were also lower on the high-fiber vegetable-based diet compared with the other 2 diets, despite a significantly greater output of total SCFA (vegetable diet, 77.8 mmol/d; starch diet, 28.5 mmol/d; and therapeutic diet, 14.7 mmol/d; $P < .001$) as a result of the greater total fecal wet weight (Table 5). There were no treatment differences in fecal butyrate concentrations.

DISCUSSION

The high-fiber vegetable and fruit diet greatly increased fecal bulk and bile acid losses, while producing dramatic reductions in serum lipid risk factors for cardiovascular disease.[43] At the same time, the concentration of bile acids was reduced as a result of the increased fecal bulk. The very large fecal bile acid concentrations would therefore not be seen as increasing the risk of colon cancer.[44]

Studies comparing lacto-ovo vegetarians and vegans (who consume no animal products) have shown markedly lower serum lipids in the vegans, similar to the differences seen between the vegetable and therapeutic diets.[45] Studies of vegetarian diets have attributed some of the cholesterol lowering specifically to the pectin component of soluble fiber found in fruit and vegetables,[46] because this viscous soluble fiber has

been shown to lower serum cholesterol.[23] Viscous fibers increase fecal bile acid losses[47] and chenodeoxycholic acid synthesis[48] and appear to be the best substantiated mechanisms by which fiber lowers serum cholesterol.[49] Very large losses of fecal bile acids on the vegetable diet may therefore have been related, in part, to the pectin fiber content of the diet[46] or the sheer bulk of food passing through the gastrointestinal tract. Increased chenodeoxycholate and cholate synthesis rates were seen on the vegetable diet. The resulting reduction in hepatic cellular cholesterol concentration would lead to upregulation of the LDL receptor, increased hepatic cholesterol uptake, and the reduction in serum levels as observed. Other factors, which may have contributed to the cholesterol-lowering effect of the high-fiber vegetable and fruit diet, were the high intake of plant sterols, vegetable proteins, and the use of nuts.[50-52] Combined, these resulted in a cholesterol reduction equivalent to a therapeutic dose of a statin,[53] the standard therapy for hyperlipidemia, and normally not achieved with dietary modification.

All protein in the high-fiber vegetable diet (123 g/d) was vegetable protein compared with 56% on the starch-based diet and 24% on the low-fat therapeutic 2 diet. A recent meta-analysis of vegetable protein feeding studies indicated a possible 0.23 mmol/L reduction in LDL cholesterol at a mean soy protein intake of 25 g daily,[50] the only vegetable protein source studied in detail so far.

Our subjects ate an average of 67 g nuts daily. These foods contain both vegetable protein and fiber and have a good dietary fatty acid profile. Consumption of 84 to 100 g nuts daily has been associated with 10% to 20% reductions in serum cholesterol.[51,52]

The high-fiber vegetable diet provided almost 1 g of plant sterols daily. Studies have shown that plant sterols, β-sitosterol and β-sitostanol, reduce serum cholesterol and the LDL cholesterol to HDL cholesterol ratio,[54,55] possibly through reducing cholesterol absorption.[56] The high-fiber vegetable diet resulted in greater fecal cholesterol and bile acid outputs than the other 2 diets. Urinary mevalonate excretion was also greater on the high-fiber vegetable diet compared with the control indicating increased cholesterol biosynthesis to replenish the increased sterol loss.[57] There was no evidence of high-fecal propionate levels or reduced insulin secretion as indicated by reduced urinary C-peptide output to explain the lower cholesterol levels on the high-fiber vegetable diet.

The present study was of short duration. Nevertheless, dramatic serum lipid changes were seen during the first week of the high-fiber vegetable diet that were maintained almost unchanged during the second week, suggesting that a maximum reduction had been achieved.

On a gram for gram basis compared with the therapeutic diet, the high-fiber vegetable and fruit diet increased fecal weight by 8.5 g/g of additional fiber, and the cereal and legume diet resulted in an increase in fecal weight of 5 g/g of additional fiber. In whole foods, additional factors, including resistant starch, nonabsorbable sugars and oligosaccharides, and a range of phytochemicals may all contribute to fecal bulk. However, the fecal bulking on the vegetable diet was marked. Wheat fiber has been reported to increase fecal bulk by 3 to 6 g/g fiber[58,59] making it one of the most effective natural fecal bulking agents. Purified vegetable fibers, which are readily fermented in the colon, are considered significantly less effective than wheat bran.[58] The purified fruit fiber pectin as kaolo-pectate is used as an antidiarrheal agent. The effect of the high-fiber whole vegetable and fruit diet is therefore the more remarkable, because the fecal outputs observed in the men are the highest that we are aware of in the literature in response to a dietary intervention in healthy subjects.

The high-fecal bulk was associated with increased fecal water content on the high-vegetable fiber diet, so diluting out bile acids and reducing a purported risk factor for colonic cancer.[24] This dilution was achieved despite an extremely high-fecal bile acid loss. However, no treatment differences were observed in pH, or the ratios of lithocholate to deoxycholate, or deoxycholate to cholate, in which high ratios have also been suggested to be associated with increased risk of colon cancer.[60] Furthermore, despite the predicted increase in microbial activity and short-chain fatty acid output,[61] short-chain fatty acid concentrations also tended to be lower on the vegetable and fruit diet due to the greatly increased fecal bulk. This dilution effect was particularly true for propionate. In addition, no increase was seen in the molar ratio of butyrate that might also have had implications for improved colonic health.[62,63]

Beneficial effects on serum lipids were also seen with the high-starch diet. This diet was also relatively high in fiber from legumes, whole meal cereal flour, and grains. Legume consumption has been associated with reductions in serum cholesterol[64,65] and cereal fiber,[3,6,7] especially in the context of low-glycemic index diets,[8-10] and whole grain cereals[4,5,11] have been shown to be associated with a reduction both in the risk of cardiovascular disease and the development of type 2 diabetes in men and women.

The fiber intake on the high-fiber vegetable diet was far higher than the 20 to 30 g/d currently recommended.[66-68] However, the intake was similar to estimates for the tropical regions of sub-Sahara Africa, for example, Uganda, where intakes have been reported to be as high as 150 g/d from vegetable sources.[69] Furthermore, the great apes living in those regions may have fiber intakes more than 10-fold greater than current human recommendations for a comparable energy intake,[70] and their intakes may be more representative of consumption patterns of the hominoid ancestors of man.

Although the diets of our remote ancestors cannot be known with certainty, we selected 2 periods where there is some agreement on the major characteristics of the diets. During the Miocene era, which ended approximately 4 to 5 million years ago, before the divergence of the ancestors of man from the great apes, the diet is generally agreed to have been a high-fiber plant-based diet[17] and has also been suggested to be similar to that described for contemporary great apes[71-74] and supported by studies of wear on dentition.[17] With the development of tools, it is suggested this diet gave way to scavenging and hunting with high-protein intakes in the paleolithic period. It has also been suggested that brain development was coincident with significant ω-3 fatty acid intakes from marine and lacustrine environments.[75-77] A major feature of all these diets is that they are effectively devoid of starch. Our second diet

was therefore a starch-based or neolithic-like diet. There is more certainty that the diets of the early agricultural revolution, possibly 10,000 years ago in the neolithic period, allowed for the first time the large scale consumption of starchy foods, which still form the basis of diets in less industrialized communities today. Nevertheless, both of these diets maintained low-serum cholesterol, and it is therefore likely that serum cholesterol levels have remained low throughout most of human dietary evolution until the present time. Furthermore, the obligatory high-bile acid losses on high-fiber vegetable diets may explain the development of the high capacity of humans to synthesize cholesterol and replenish the bile acid pool, an ability with survival value in the past, but a disadvantage on contemporary western diets. These diets are notably low in fiber, vegetable proteins, and plant sterols, which would tend to lower serum cholesterol, and high in saturated and trans fatty acids, which increase hepatic cholesterol biosynthesis.

The very significant effects of high-fruit and vegetable intakes on serum lipids and laxation indicates that further studies exploring their use at high intake levels is warranted. The data support current efforts to increase consumption of these foods and suggest that attention should be paid to their long-term effects on cardiovascular and colonic health.

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