A Dietary Portfolio Approach to Cholesterol Reduction: Combined Effects of Plant Sterols, Vegetable Proteins, and Viscous Fibers in Hypercholesterolemia

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Plant sterols, soy proteins, and viscous fibers are advised for cholesterol reduction but their combined effect has never been tested. We therefore assessed their combined effect on blood lipids in hyperlipidemic subjects who were already consuming a low–saturated fat, low-cholesterol diet before starting the study. The test (combination) diet was 1 month in duration and was very low in saturated fat and high in plant sterols (1 g/1,000 kcal), soy protein (23 g/1,000 kcal), and viscous fibers (9 g/1,000 kcal) obtained from foods available in supermarkets and health food stores. One subject also completed 2 further diet periods: a low-fat control diet and a control diet plus 20 mg/d lovastatin. Fasting blood lipids, blood pressure, and body weight were measured prior to and at weekly intervals during the study. The combination diet was rated as acceptable and very filling. The diet reduced low-density lipoprotein (LDL)-cholesterol by 29.0% ± 2.7% ($P < .001$) and the ratio of LDL-cholesterol to high-density lipoprotein (HDL)-cholesterol by 26.5% ± 3.4% ($P < .001$). Near maximal reductions were seen by week 2. In the subject who took Mevacor and control diets each for 4 weeks, the reduction in LDL:HDL-cholesterol on Mevacor was similar to the combination diet. We conclude that acceptable diets of foods from supermarkets and health food stores that contain recognized cholesterol-lowering dietary components in combination (a dietary portfolio) may be as effective as the starting dose of older first-line drugs in managing hypercholesterolemia.

DIET HAS BEEN considered by some to be ineffective in the management of hypercholesterolemia.[1,2] Nevertheless, it continues to be stressed as the cornerstone for managing raised blood lipids to prevent cardiovascular disease.[3] Recently, in addition to reductions in saturated fat and dietary cholesterol, the National Cholesterol Education Program (NCEP) Panel III has recommended plant sterols (2 g/d) and viscous fibers (10 to 25 g/d) as additional dietary options to maximize the effectiveness of diet.[3] The American Heart Association (AHA) has also drawn attention to the possible benefits of soy proteins.[4] In turn, the Food and Drug Administration (FDA) has permitted health claims for coronary heart disease (CHD) risk reduction for foods delivering adequate amounts of plant sterols,[5] viscous fibers (oat β-glucan and psyllium),[6,7] and soy proteins.[8] However, it is not known whether a combination of these dietary factors will result in an addition, synergy, or quenching of their individual cholesterol-lowering effects. Nevertheless, their proposed modes of action are different, involving increased bile acid losses for viscous fibers,[9-11] increased fecal cholesterol losses for plant sterols,[12,13] and reduced hepatic cholesterol synthesis and increased low-density lipoprotein (LDL) receptor-mediated cholesterol uptake for soy proteins.[14,15]

In view of the differences in possible mechanisms of action and the fact that each agent in acceptable doses may reduce serum cholesterol by 5% to 10%,[16-20] it was assumed that their effects were likely to be additive and that in combination a clinically significant reduction in serum cholesterol could be achieved. This effect may be especially relevant in subjects with lipid concentrations or risk factors just below the cut-off point for drug therapy and for those with muscle tenderness or whose muscle and possibly liver enzyme responses to drug therapy preclude the use of conventional drugs. We therefore studied a group of hyperlipidemic subjects who had taken part in previous studies and were familiar with diet study protocols. These subjects were endeavoring to comply with an NCEP step 2 diet and were provided with the combination diet for 1 month to assess efficacy and acceptability.

MATERIALS AND METHODS

Subjects

Thirteen subjects (7 men and 6 postmenopausal women), age (mean ± SE) 65 ± 3 years (range, 43 to 84 years), with a body mass index (BMI) of 25.6 ± 0.9 kg/m^2 (range, 20.6 to 30.7 kg/m^2) and baseline LDL-cholesterol of 4.50 ± 0.20 mmol/L (range, 3.45 to 6.61 mmol/L) were recruited from patients attending the Risk Factor Modification Center, St. Michael's Hospital. All subjects had taken part in previous dietary studies, were experienced in following dietary protocols, and previously had raised LDL-cholesterol levels (>4.1 mmol/L).[3] At the time of the study, 5 subjects had raised LDL-cholesterol levels, 1 subject had raised triglyceride levels (>2.30 mmol/L), 3 subjects had both raised cholesterol and triglyceride levels, 1 subject had a low high-density lipoprotein (HDL)-cholesterol concentration (<0.9 mmol/L), and 3 subjects had blood lipids in the normal range.[3] No subjects had a history of diabetes, renal or liver disease, and none were taking medications known to influence serum lipids. One subject took antihistamines for a cough in the third week of the study and another subject took anti-inflammatory drugs in the second week of the run-out. Both subjects were excluded from the assessment of C-reactive protein. One subject completed only 3 weeks and withdrew due to

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Table 1. Calculated Macronutrient Intakes (mean ± SE) During the Run-in, Test, and Run-out Phases of the Portfolio Study

	Run-in (week 0)	Portfolio Diet (mean of weeks 2 to 4)	Run-out (week 6)
No. of subjects	12	13	12
Energy (kcal/d)	1,703 ± 120[a]	1,999 ± 118[b]	1,703 ± 104[a]
Total protein (% of protein)	17.3 ± 0.8[a]	22.4 ± 0.5[b]	18.1 ± 0.8[a]
Vegetable protein (% of protein)	48.7 ± 3.5[b]	96.8 ± 0.2[c]	39.1 ± 2.8[a]
Available carbohydrate (% of energy)	52.9 ± 2.8[ab]	50.6 ± 0.6[a]	58.2 ± 1.3[b]
Total dietary fiber (g/1,000 kcal)	17.1 ± 1.9[a]	30.7 ± 1.0[b]	17.8 ± 1.8[a]
Total fat (% of energy)	28.3 ± 2.5	27.0 ± 0.8	22.7 ± 1.5
SFA (% of energy)	7.7 ± 0.7[b]	4.3 ± 0.1[a]	6.2 ± 0.7[ab]
MUFA (% of energy)	11.9 ± 1.6	11.8 ± 0.5	9.0 ± 0.7
PUFA (% of energy)	6.0 ± 0.4[a]	9.9 ± 0.2[b]	5.3 ± 0.5[a]
Dietary cholesterol (mg/1,000 kcal)	99 ± 13[b]	10 ± 3[a]	79 ± 9[b]
Alcohol (% of energy)	1.5 ± 0.5[b]	0.2 ± 0.1[a]	1.0 ± 0.4[ab]
Satiety (−3 to +3)	1.3 ± 0.2[a]	2.9 ± 0.2[b]	1.3 ± 0.3[a]

NOTE. Values on the same row not sharing a common superscript are significantly different.
Abbreviations: SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

dyspepsia associated with *Helicobacter pylori* infection requiring antibiotic therapy.

Dietary advice on low–saturated fat (<7% dietary calories) and low-cholesterol diets (<200 mg/d) had been reinforced on at least 2 occasions over the previous year and at entry to the study 6 subjects recorded diets with less than 7% (total energy) saturated fat and 9 subjects took diets with less than 200 mg/d cholesterol.

Study Protocol

Subjects were monitored on their own low–saturated fat therapeutic diets for one week prior to the start of the study, and for a further 2 weeks after the study on return to their low–saturated fat therapeutic diets. During the middle 4 weeks subjects took the combination diet when all foods were provided with the exception of fresh fruit and most vegetables (okra was provided). Blood samples and body weights were obtained after a 12-hour overnight fast at weekly intervals and during week 2 of the washout. On each clinic visit, blood pressure was measured in the nondominant arm by the same 2 observers. Seven-day weighed diet histories were obtained for the week prior to and 2 weeks following the combination diet. Completed menu check lists were returned at weekly intervals during the 4-week combination diet period.

At weekly intervals subjects recorded their overall feeling of satiety on the diet using a 7-point bipolar semantic scale where -3 was extremely hungry, 0 was neutral, and +3 was the stage of satiety just prior to discomfort. At the end of the study, subjects were also asked if the combination diet, possibly with minor modifications, would be acceptable as the subjects' routine diet. Responses were recorded on a 11-point semantic scale where 0 was totally unacceptable, 5 was acceptable with minor modifications to form the regular diet (ie, sustainable), and 10 was highly desirable without modification.

One subject undertook 2 additional 1-month phases separated by 2-week washout periods. These consisted of a control diet (low saturated fat/low dietary cholesterol with the same macronutrient profile as the combination diet) and the control diet taken with 20 mg/d of a statin (lovastatin) to allow the combination diet to be compared directly with drug therapy.

The study was approved by the Ethics Committee of the University of Toronto and St. Michael's Hospital and informed consent was obtained from the subjects.

Diets

The diets eaten before and after the 4-week combination diet were the subjects' routine therapeutic low-fat diets, which approximated to NCEP Step 2 guidelines (≤7% energy from saturated fat and <200 mg/d dietary cholesterol) (Table 1).[3] Subjects were provided with self-taring electronic scales and asked to weigh all food items consumed during the study period. During the combination diet period, all foods to be consumed by the subjects were provided at weekly clinic visits with the exception of fruit and low-calorie vegetables, such as non–starch-containing vegetables including broccoli, carrots, red peppers, tomato, onions, cauliflower, okra (provided), and eggplant, which subjects were instructed to obtain from their local stores. Subjects were provided with a 7-day rotating menu plan including specified fruit and vegetables on which they checked off each item as eaten and confirmed the weight of the foods. The same menu plan was used for all subjects but was modified to suit individual preferences providing the goals for viscous fiber, soy protein, plant sterol, and almond consumption were met. The basic menu plan is given in Table 2. For ease of consumption, where possible, items were prescribed in whole units (eg, cup of instant soup, or 1 frozen dinner, container of whole soy yogurt, soy deli slice, soy burger, or dog etc).

The aim of the combination diet was to provide 1 g plant sterols per 1,000 kcal as an enriched margarine; 8.2 g viscous fibers per 1,000 kcal from oats, barley, and psyllium; and 22.7 g soy protein per 1,000 kcal. Raw unblanched almonds also provided vegetable protein (2.9 g/1,000 kcal). Emphasis was placed on eggplant and okra as additional sources of viscous fiber (0.55 g/1,000 kcal and 0.67 g/1,000 kcal, respectively). Thus, 200 g eggplant and 100 g okra were prescribed to be eaten on a 2,000-kcal diet each day. Oats were consumed as cooked oat bran cereal and an oat bran bread containing only oatbran and gluten. Barley grains were boiled and eaten in place of rice. Psyllium was taken with water or mixed into soy milk or yogurt as unflavored Metamucil (Procter and Gamble, Toronto, Canada). Soy protein was provided as soy milk, soy sausages, soy cold cuts, and soy burgers (Too Good To Be True, Loblaw Brands, Toronto, Canada). Additional vegetable protein was provided as beans, chick peas, and lentils, consumed plain or as an ingredient in frozen dinners and instant soups.

The control diet for the subject who undertook three 1-month studies was a low-fat diet with the same macronutrient and fatty acid profile as the combination diet but lacking the sources of viscous fibers and plant sterols and where skim milk products replaced the soy and vegetable protein sources in the combination diet. Weight-maintaining diets were provided based on estimated caloric requirements.

Compliance was assessed from the completed weekly check lists and from the return of uneaten food items.

Table 2. One-Day Menu Plan for Combination Diet for a 2,000-kcal Diet With Alternatives (as superscripts) Provided on Other Days of the Week

Breakfast	Snack	Lunch	Snack	Dinner	Snack
35 g Oatbran	14 g Almond	65 g Vegetarian chili[5]	14 g Almond	295 g Vegetable curry[7]	175 g Soyagurt
150 g Orange[1]	250 g Soy milk	67 g Oatbran bread	7 g Metamucil	85 g Soy burger[8]	7 g Metamucil
7 g Metamucil[9]		17 g Margarine	250 g Soy milk	80 g Northern beans[3]	10 g Double-fruit jam
33 g Oatbran bread		62 g Soy deli slices[6]		35 g Barley[4]	
8 g Margarine[10]		80 g Tomato		100 g Okra	
18 g Double fruit jam		150 g Orange[1]		200 g Eggplant	
250 g Soy milk				200 g Cauliflower[2]	
				80 g Onions	
				60 g Red pepper	

NOTE. All weights given are precooked weights. Foods could be redistributed throughout the day to suit personal preferences

[1]Fruit alternatives: apple, pear.

[2]Vegetable alternatives: broccoli, carrot.

[3]Legume alternatives (canned): kidney bean, lentils, chickpeas

[4]Four times a week.

[5]Lunch, soup alternatives: Lentil with curry, vegetable barley, black bean, minestrone and pasta.

[6]Lunch, soy alternative: hot dogs.

[7]Dinner, frozen meal (4 times a week) alternative: 3-bean chili.

[8]Dinner, soy alternatives: ground soy, tofu.

[9]Taken each time in 250 mL of water.

[10]Plant sterol margarine.

Analyses

Serum was analyzed according to the Lipid Research Clinics protocol[21] for total cholesterol, triglyceride, and HDL-cholesterol, after dextran sulfate–magnesium chloride precipitation.[22] All samples from a given individual were analyzed in the same batch. LDL-cholesterol was calculated.[23] Serum apolipoprotein A-l and B were measured by nephelometry[24] and lipoprotein(a) [Lp(a)] was measured with a commercial enzyme linked immunosorbant assay [Macra Lp(a) Kit, Trinity Biotech USA, Jamestown, NY].

Oxidized LDL was measured as conjugated dienes in the LDL fraction after isolation of LDL particles by precipitation with buffered heparin at their isoelectric point.[25] The results were expressed as total serum conjugated dienes in the LDL fraction.[26]

Serum samples, stored at -70°C, were analyzed for C-reactive protein by end-point nephelometry (Behring BN-100, N high sensitivity C-reactive protein reagent, Dade-Behring, Mississauga, Canada).

Total L-homocysteine was measured in citrated plasma, which had been stored in the refrigerator at 2°C for approximately 1.5 hours prior to separation, using a fluorescence polarization immunoassay (IMx Homocysteine assay, Axis-Shield, Oslo, Norway).

Red blood cell fragility was assessed on fresh red blood cells collected in vacutainer tubes containing EDTA (Becton Dickinson, Mississauga, Canada); 0.2 mL packed red blood cells were added to 2 mL unbuffered saline covering the range of sodium chloride concentrations from 0.20 to 0.70 g/L in 0.05-g/L increments. After 3 hours, the cells were centrifuged at 1,000 $\times$ *g* at room temperature for 5 minutes and the supernatant was read at 520 nm.[27]

Diets were analyzed using a program based on US Department of Agriculture data[28] with additional data on foods analyzed in the laboratory for protein, total fat, and dietary fiber using American Association of Analytical Chemists (AOAC) methods.[29] Fatty acids were analyzed by gas chromatography.[11] Additional dietary fiber values were obtained from the tables of Anderson and Bridges.[30]

Statistical Analysis

The results were expressed as means $\pm$ SE. Analysis of variance was used to determine whether there was a significant F value in the comparison of weeks 2, 3, and 4 of the combination diet. In the absence of a significant F value the restricted mean of weeks 2, 3, and 4 was used as the combination treatment value.[31] The significance of the differences between the pretreatment diet, combination diet, and posttreatment diet was assessed by the least squares means test with Tukey adjustment (PROC MIXED/SAS 8.2).[31] The model used had the treatment value as the response variable and week and week by sex as main effects and a random term corresponding to subject nested within sex. Student's paired *t* test (2-tailed) was used to assess the significance of the percentage change from pretreatment. The Hegsted[32] equation was used to predict the changes in serum cholesterol resulting from alterations in dietary fatty acid and cholesterol intakes. The Framingham 10-year cardiovascular disease risk equation was applied to the data using systolic blood pressure, age, sex, and LDL:HDL cholesterol values.[33] No subjects smoked or had evidence of diabetes or left ventricular hypertrophy. The concentration required to obtain 50% hemolysis was determined assuming a linear response between consecutive observations. For each subject, the maximum optical density obtained from both tests combined represented the 100% hemolysis value for that subject.

RESULTS

In the majority of subjects, compliance in terms of caloric intake was good at 92.5% $\pm$ 2.9%. The overall rating of the diet was 6.3 $\pm$ 0.6 (scale 0 to 10), which was significantly above 5.0, the level at which diet was acceptable with minor modifications ($P = .043$). Nine of the thirteen subjects stated that they would be willing to continue the combination diet, possibly with small modifications, as their therapeutic diets. All subjects considered that they were eating as much food as they were capable without experiencing discomfort (satiety rating, 2.9 $\pm$ 0.2 *v* 1.3 $\pm$ 0.2 at week 0, $P = .002$; scale -3 to +3). Throughout the period of observation subjects tended to lose weight: -0.10 ± 0.05 kg/wk ($P = .127$) over the combination diet; and -0.2 ± 0.05 kg/wk ($P = .001$) during the run-out phase.

Table 3. CHD Risk Factors at Baseline, on the Combination Diet, and During the Run-out Period (n = 13)

	Baseline (Week 0)	Mean Treatment (Weeks 2-4)	Run-out (Week 6)
Body weight (kg)*	69.9 ± 3.6[a]	69.5 ± 3.5[a]	68.3 ± 3.7[a]
Cholesterol*			
Total-cholesterol (mmol/L)	6.46 ± 0.21[a]	5.01 ± 0.20[c]	5.90 ± 0.22[b]
LDL-cholesterol (mmol/L)	4.22 ± 0.11[a]	3.01 ± 0.17[c]	3.80 ± 0.20[b]
HDL-cholesterol (mmol/L)	1.37 ± 0.11[a]	1.34 ± 0.11[a]	1.35 ± 0.12[a]
Triglycerides (mmol/L)*	1.92 ± 0.35[a]	1.45 ± 0.18[a]	1.65 ± 0.28[a]
Apolipoproteins*			
Apo A-I (g/L)	1.70 ± 0.07[a]	1.61 ± 0.08[a]	1.64 ± 0.08[a]
Apo B (g/L)	1.32 ± 0.05[a]	1.01 ± 0.05[b]	1.25 ± 0.06[a]
Ratios*			
Total-C:HDL-C	5.06 ± 0.41[a]	4.00 ± 0.30[b]	4.69 ± 0.36[a]
LDL-C:HDL-C	3.31 ± 0.26[a]	2.45 ± 0.24[b]	3.03 ± 0.26[a]
Apo B:Apo A-I	0.80 ± 0.05[a]	0.64 ± 0.05[b]	0.78 ± 0.05[a]
LDL conjugated dienes (μmol/L)†‡	47.9 ± 4.2[a]	31.0 ± 1.9[b]	46.0 ± 3.6[a]
Homocysteine (μmol/L)‡	6.9 ± 0.5[a]	7.1 ± 0.4[a]	7.6 ± 0.2[a]
Lp(a) (mg/dL)*	11.5 ± 3.0[a]	12.4 ± 3.5[a]	12.7 ± 3.3[a]
C-reactive protein (mg/L)*¶	1.81 ± 0.55[a]	1.26 ± 0.51[a]	1.12 ± 0.46[a]
Blood pressure (mm Hg)*			
Systolic	117 ± 4[a]	114 ± 3[a]	117 ± 3[a]
Diastolic	70 ± 3[a]	69 ± 2[a]	70 ± 2[a]
Calculated CHD risk (10 yr %)‖	10.3 ± 1.2[a]	7.3 ± 1.1[b]	9.2 ± 1.4[a]

NOTE. Values on the same row not sharing a common superscript are significantly different ($P < .050$). Treatment values represent the mean of: *weeks 2, 3, and 4; or †Week 2 and 4 alone. 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 100.

‡As conugated dienes (μmol) in the LDL fraction.

¶Data from 11 subjects only.

‖CHD risk calculated using the Framingham cardiovascular disease predictive equation.[33]

Blood Lipids

Significant reductions in blood lipids were seen during the combination diet compared to the run-in and run-out periods (Table 3). At the end of the combination diet, the blood lipid reductions from baseline were: total cholesterol, 22.3% ± 2.0%, $P < .001$; LDL-cholesterol, 29.0% ± 2.7%, $P < .001$; apolipoprotein B, 24.2% ± 2.0%, $P < .001$; total:HDL-cholesterol, 19.8% ± 2.9%, $P < .001$; LDL:HDL-cholesterol, 26.5% ± 3.4%, $P < .001$; and apolipoprotein B:A-I, 19.7% ± 2.7%, $P < .001$ (Fig 1). The reduction in calculated CHD risk[33] was 30.0% ± 4.6% ($P < .001$). The predicted reduction in serum cholesterol[32] based on the change in dietary fatty acid and cholesterol intake was 9.3% ± 1.1% on the combination diet. The difference between the observed and predicted reduction in serum cholesterol was 13.3% ± 2.5% ($P < .001$), attributable to the viscous fiber, soy protein, and plant sterols.

The 2-week run-out post–combination diet LDL-cholesterol values were still 10.1% ± 3.8% ($P = .022$), below the pretreatment values (Fig 1). The data for the subject who completed 3 phases indicated that the statin and combination phases produced similar reductions in the ratios of total:HDL and LDL:HDL-cholesterol (Fig 2).

Subgroup assessment of subjects who at the start of the combination diet had either normal lipids, raised LDL-cholesterol alone, raised triglyceride alone, raised LDL-cholesterol and triglyceride combined, or low HDL-cholesterol all demonstrated large reductions in total and LDL-cholesterol and calculated CHD risk in response to the combination diet (Table 4). Simple classification according to raised or normal LDL-cholesterol at the start of the diet indicated a very similar response to the dietary intervention, including calculated CHD risk, which was independent of starting LDL cholesterol level (Table 5).

Lp(a), Homocysteine, C-Reactive Protein, Oxidized LDL, Blood Pressure, and Red Blood Cell Fragility

For the 11 subjects, who took no antihistamine or anti-inflammatory medications, C-reactive protein values tended to be lower on the combination diet (23.4% ± 12.1%, $P = .081$). When the run-out data were also included, the post-baseline reduction in C-reactive protein was significant (25.5% ± 11.4%; $P = .048$). Oxidized LDL levels measured as conjugated dienes in the LDL fraction were reduced by 32.9% ± 12.3% ($P < .001$) with no change in the ratio of oxidized LDL to cholesterol in the LDL fraction. No significant differences were seen in Lp(a), homocysteine ($P = .096$), or blood pressure between the mean pretreatment diet, the combination diet, and the post–combination diet values (Table 3). No significant difference was seen in red blood cell fragility between pretreatment and week 4 of the combination diet (saline concentration for 50% hemolysis, 0.437 ± 0.006 g/100 mL *v* 0.442 ± 0.006 g/100 mL, $P = .250$).

DISCUSSION

A combination of dietary components appeared to be additive in effect in reducing serum LDL-cholesterol by 29% and

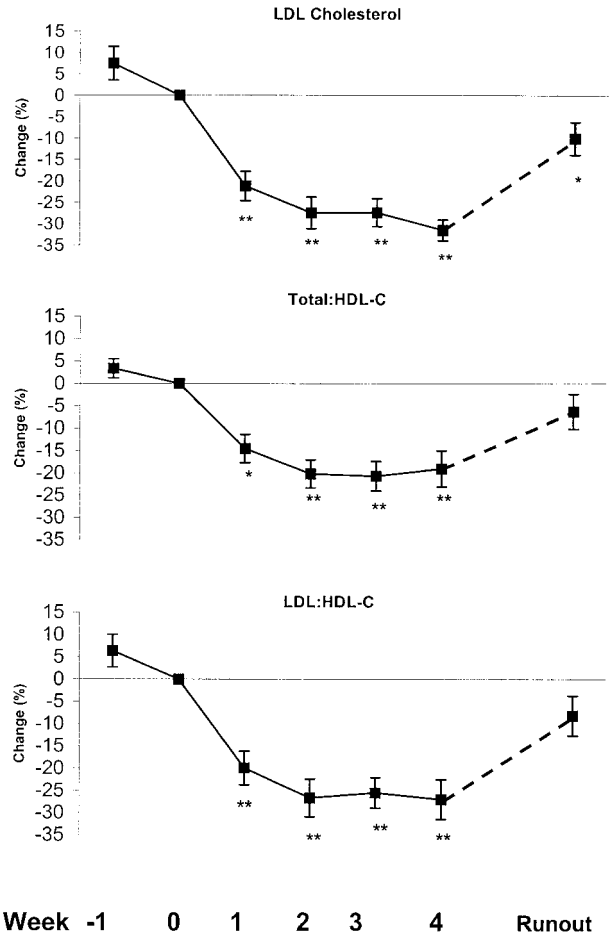

Fig 1. Percent change from baseline in LDL-cholesterol and the ratios of total:HDL and LDL:HDL on the combination diet (n = 13). Values are means ± SE. Significantly different from baseline: *$P <$ .05; **$P \leq$ .001.

the LDL:HDL-cholesterol ratio by 27%. The effect achieved with a combination of plant sterols, viscous fibers, and vegetable proteins from readily available foods was of similar magnitude to that achieved with the starting dose of the older statins,[34] which for many years have been the first-line drug therapy for hypercholesterolemia. A small part of the reduction in serum cholesterol could be the result of displacement of foods containing saturated fat and dietary cholesterol. This effect of improving diet by displacement is a potential advantage of this dietary combination approach over drug therapy.

Although the foods were rated as palatable they were considered very filling. In practice, excess energy intake is associated with a worsening of the blood lipid profile, obesity, and increased CHD risk.[35] The satiety effect of the diet may therefore be a further advantage of the combination diet.

The present dietary approach is likely to be of value for those patients who, after reducing saturated fat and dietary cholesterol intakes, maintain an LDL-cholesterol above 4.1 mmol/L or for patients for whom, in the absence of other risk factors, drugs may not be prescribed.[3] Nevertheless, it is in this group and those with lower lipid levels that a significant number of heart attacks occur.[36] Furthermore, there are individuals who are reluctant to take medications and patients in whom elevations of muscle and liver enzymes on medications make physicians concerned in maintaining them on statin therapy.

The one subject who took the 3 diets, which allowed a direct comparison of the combination diet with a statin, demonstrated a similar reduction in blood lipids despite the fact that the statin was taken with a diet equivalent to the combination diet in terms of saturated fat and cholesterol content. Further studies are required to confirm this comparison.

The value of statins is not related simply to their cholesterol-lowering properties but to their pleotrophic effects. Statins have been shown to have anti-inflammatory properties important in CHD risk reduction.[37] The combination diet also tended to reduce C-reactive protein levels. Since individually none of the components of the combination diet have been shown to reduce C-reactive protein, the question remains of whether effective reduction of serum cholesterol per se reduces C-reactive protein. In view of the many beneficial effects of statins it will be necessary to demonstrate further cardiovascular benefits for diet in addition to cholesterol reduction before equivalency between diet and statins can be assumed.

It was hoped that the combination diet would show a reduction in both the total oxidized LDL and the ratio of oxidized LDL to cholesterol in the LDL fraction. This was predicted from previous studies with soy protein, which is also a component of the combination diet.[38,39] In the present study, the oxidized LDL, as conjugated dienes in the LDL fraction, was

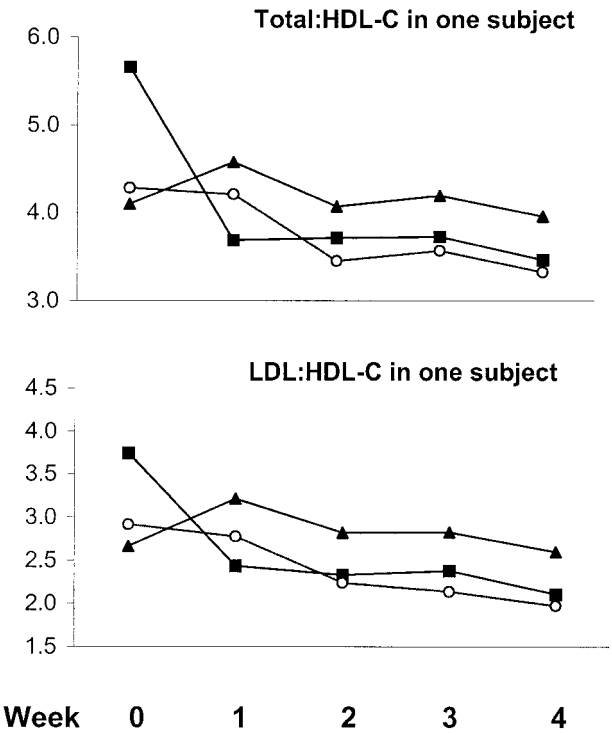

Fig 2. Change from baseline in the ratios of total:HDL and LDL:HDL in 1 subject who took 3 diets: the combination diet (■), an NCEP Step 2 diet (○), and the NCEP Step 2 diet plus a statin (▲).

Table 4. CHD Risk Factors at Baseline and Percentage Change From Baseline at End of Combination Diet: Subgroup Analysis

		Normal (n = 3)	Triglycerides > 2.2 (n = 1)	HDL < 0.9 (n = 1)	LDL > 4.1 (n = 5)	Triglycerides + LDL (n = 3)
Cholesterol						
Total-C (mmol/L)	Baseline week 0	6.0	6.6	5.3	6.3	7.5
	Percent change	−14.1	−29.5	−25.3	−26	−21.1
	P	.007	—	—	.001	.055
LDL-C (mmol/L)	Baseline week 0	3.9	3.9	3.5	4.3	4.7
	Percent change	−25.4	−44.7	−29.8	−32.9	−20.8
	P	.003	—	—	.001	.080
Apolipoproteins						
Apo B (g/L)	Baseline week 0	1.2	1.4	1.2	1.3	1.6
	Percent change	−20.9	−34.1	−24.9	−25.6	−21.9
	P	.015	—	—	.002	.049
Ratios						
Total-C:HDL-C	Baseline week 0	3.7	5.1	6.5	4.5	6.8
	Percent change	−15.8	−32.3	−26.6	−14.9	−25.5
	P	.163	—	—	0.017	.058
LDL-C:HDL-C	Baseline Week 0	2.4	3.1	4.3	3.2	4.2
	Percent change	−26.7	−46.1	−31.1	−22.5	−25.2
	P	.046	—	—	.020	.087
Apo B:Apo A-I	Baseline week 0	0.6	0.8	0.9	0.8	1
	Percent change	−21.1	−27.6	−20.1	−18.7	−17.3
	P	.043	—	—	.018	.194
LDL conjugated dienes (μmol)*	Baseline week 0	39.0	52.0	50.4	39.4	69.0
	Percent change	−24.0	−30.4	−56.4	−29.7	−40.0
	P	.030	—	—	.002	.034
Calculated CHD risk (10 yr %)†	Baseline week 0	7.1	10.2	15.6	10.6	11.3
	Percent change	−18.9	−68.3	−27.4	−27.0	−34.1
	P	.100	—	—	.014	.035

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 100.

*As conjugated dienes (μmol) in the LDL fraction.

†CHD risk calculated using the Framingham cardiovascular disease predictive equation.[33]

reduced but only in proportion to the reduction in LDL-cholesterol. Larger numbers of subjects may be required to detect an effect on the ratio of conjugated dienes to cholesterol in the LDL fraction.

The dietary components selected were all well recognized for their cholesterol-lowering properties.[5-20,40-46] Meta-analyses have suggested reductions in serum LDL-cholesterol of 12.5% for 45 g/d soy protein[19]; 6% to 7% for 9 to 10 g/d psyllium,[16,17] with smaller reductions for other viscous fibers[18]; and 10% for 1 to 2 g plant sterol/d.[20] These data come from studies with background diets higher in saturated fat and cholesterol than in the present study. In studies of soy at lower intakes of saturated fat, in which subjects in the present study also took part, smaller reductions in cholesterol of 4% for 52 g/d of soy protein were seen.[47] Similarly, plant sterols have also been shown to be less effective in diets lower in saturated fat and cholesterol.[48]

We therefore predicted a 15% to 20% reduction in serum cholesterol if the effects of the 3 components were additive. The lower saturated fat and cholesterol intakes accounted for a further 9% reduction.[32] Therefore, the total reduction was predicted to be 25% to 30%, close to the 22% observed. This observation is supported by the similarity in cholesterol lowering achieved by the combination diet and the statin in the 1 subject who took these treatments. These data will encourage use of dietary combinations in the future to maximize the effectiveness of diet and allow for inclusion of further foods with promising new dietary components such as Chinese red rice, containing hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors,[49] and garlic with allicin.[50]

It has been suggested that plant sterols may increase the risk of hemorrhagic stroke.[51] This suggestion is based on studies of spontaneously hypertensive stroke prone rats.[27] The increased risk has been proposed to be due to increased cell fragility resulting from the absorption of small amounts of plant sterols.[52] Increased red blood cell fragility has been observed in rats fed plant sterols.[51] We found no major difference in the saline concentration at which hemolysis took place between bloods obtained at baseline versus 1 month after supplementation with plant sterols in otherwise healthy hyperlipidemic subjects.

Low-fat, high-glycemic load diets of the kind often prescribed for cardiovascular disease have been criticized for their relative lack of effect.[2] To increase effectiveness, the focus has turned more specifically to saturated fat reduction of less than 7% of total calories.[3] There is also now a recognition that other features of diet such a plant sterols, viscous fibers,[3] soy proteins,[4] and, more recently, nuts have also been shown to be advantageous.[43,44,53] Inclusion of these foods in combination not only adds to the cholesterol-reducing potential of the diet

Table 5. CHD Risk Factors at Baseline and Percentage Change From Baseline to End of Combination Diet in Subjects With Normal (n = 5) or Raised LDL-Cholesterol

		Baseline Week 0	Percent Change	*P*
Cholesterol				
Total-C (mmol/L)	Normal	6.0 ± 0.2	−19.4 ± 3.4	0.004
	LDL > 4.1	6.8 ± 0.3	−24.1 ± 2.5	0.000
LDL-C (mmol/L)	Normal	3.8 ± 0.1	−30.1 ± 3.8	0.001
	LDL > 4.1	4.5 ± 0.1	−28.4 ± 3.9	0.000
HDL-C (mmol/L)	Normal	1.4 ± 0.2	4.7 ± 5.0	0.403
	LDL > 4.1	1.3 ± 0.1	−5.0 ± 4.8	0.330
Triglycerides (mmol/L)	Normal	1.7 ± 0.4	−3.6 ± 22.1	0.880
	LDL > 4.1	2.1 ± 0.5	−19.1 ± 8.6	0.062
Apolipoproteins				
Apo A-I (g/L)	Normal	1.7 ± 0.1	−2.4 ± 3.0	0.457
	LDL > 4.1	1.7 ± 0.1	−6.5 ± 3.5	0.107
Apo B (g/L)	Normal	1.2 ± 0.0	−24.3 ± 2.9	0.001
	LDL > 4.1	1.4 ± 0.1	−24.2 ± 2.8	0.000
Ratios				
Total-C:HDL-C	Normal	4.5 ± 0.6	−21.3 ± 5.3	0.016
	LDL > 4.1	5.4 ± 0.6	−18.8 ± 3.6	0.001
LDL-C:HDL-C	Normal	2.9 ± 0.4	−31.5 ± 5.0	0.003
	LDL > 4.1	3.6 ± 0.3	−23.5 ± 4.5	0.001
Apo B:Apo A-I	Normal	0.7 ± 0.1	−22.2 ± 2.8	0.001
	LDL > 4.1	0.8 ± 0.1	−18.1 ± 4.1	0.003
LDL conjugated dienes (μmol)*	Normal	43.9 ± 3.4	−31.8 ± 6.7	0.009
	LDL > 4.1	50.5 ± 6.6	−33.6 ± 4.0	0.000
Calculated CHD risk (10 yr %)†	Normal	9.4 ± 2.4	−30.5 ± 10.2	0.041
	LDL > 4.1	10.9 ± 1.5	−29.7 ± 4.6	0.000

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 100.

*As conjugated dienes (μmol) in the LDL fraction.

†CHD risk calculated using the Framingham cardiovascular disease predictive equation[33]

but helps to structure the diet so that less desirable foods are excluded.

We conclude that a portfolio approach of diversifying the dietary investment in a range of cholesterol-lowering components with different mechanisms of action is effective in reducing lipid risk factors for cardiovascular disease. In combination, viscous fiber from oats and psyllium, vegetable proteins emphasizing soy and almonds, and plant sterols reduce LDL-cholesterol to the same extent as the starting dose of the older statins. Plant sterols, vegetable proteins, and viscous fibers are major components of plant-based diets as currently advocated and the consumption of vegan or plant-based diets has been associated with large reductions in blood lipids in the past.[54,55] It is also possible that, as with the statins, these diets will have pleotrophic effects, including anti-inflammatory effects.

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