Effects of Reducing Dietary Saturated Fatty Acids on Plasma Lipids and Lipoproteins in Healthy Subjects

The Delta Study, Protocol 1

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Abstract—Few well-controlled diet studies have investigated the effects of reducing dietary saturated fatty acid (SFA) intake in premenopausal and postmenopausal women or in blacks. We conducted a multicenter, randomized, crossover-design trial of the effects of reducing dietary SFA on plasma lipids and lipoproteins in 103 healthy adults 22 to 67 years old. There were 46 men and 57 women, of whom 26 were black, 18 were postmenopausal women, and 16 were men ≥40 years old. All meals and snacks, except Saturday dinner, were prepared and served by the research centers. The study was designed to compare three diets: an average American diet (AAD), a Step 1 diet, and a low-SFA (Low-Sat) diet. Dietary cholesterol was constant. Diet composition was validated and monitored by a central laboratory. Each diet was consumed for 8 weeks, and blood samples were obtained during weeks 5 through 8. The compositions of the three diets were as follows: AAD, 34.3% kcal fat and 15.0% kcal SFA; Step 1, 28.6% kcal fat and 9.0% kcal SFA; and Low-Sat, 25.3% kcal fat and 6.1% kcal SFA. Each diet provided ≈275 mg cholesterol/d. Compared with AAD, plasma total cholesterol in the whole group fell 5% on Step 1 and 9% on Low-Sat. LDL cholesterol was 7% lower on Step 1 and 11% lower on Low-Sat than on the AAD (both $P<.01$). Similar responses were seen in each subgroup. HDL cholesterol fell 7% on Step 1 and 11% on Low-Sat (both $P<.01$). Reductions in HDL cholesterol were seen in all subgroups except blacks and older men. Plasma triglyceride levels increased ≈9% between AAD and Step 1 but did not increase further from Step 1 to Low-Sat. Changes in triglyceride levels were not significant in most subgroups. Surprisingly, plasma Lp(a) concentrations increased in a stepwise fashion as SFA was reduced. In a well-controlled feeding study, stepwise reductions in SFA resulted in parallel reductions in plasma total and LDL cholesterol levels. Diet effects were remarkably similar in several subgroups of men and women and in blacks. The reductions in total and LDL cholesterol achieved in these different subgroups indicate that diet can have a significant impact on risk for atherosclerotic cardiovascular disease in the total population. **(*Arterioscler Thromb Vasc Biol*. 1998;18:441-449.)**

Key Words: lipids ■ lipoproteins ■ cholesterol ■ diet ■ saturated fat

The classic studies by Hegsted et al[1] and Keys et al[2] were the first to demonstrate that changes in dietary fat and cholesterol are associated with changes in plasma total cholesterol. Those studies, however, were carried out in groups of middle-aged white men and measured only total cholesterol levels. Although numerous publications demonstrating that reductions in dietary SFAs and cholesterol are associated with lowering of plasma total and LDL cholesterol have appeared since the work of Hegsted and Keys, many of those studies have compared diets with extreme differences in these constituents.[3,4] Hegsted et al[5] recently reported that a large compilation of more recent investigations supported the earlier work of his group and that of Keys and his colleagues: we are still forced, however, to extrapolate from their results when we make decisions relevant to diet and health. In particular, because most investigations directly addressing the effects of diets on plasma lipids have used white men, we do not have adequate information about the efficacy of the Step 1 diet, which is advocated by the American Heart Association, the NCEP, and the American Diabetes Association, in a broad spectrum of the American public.[6–15] In addition, although survey data are available concerning nutrient intake of women, other racial groups, children, and the elderly, few

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Selected Abbreviations and Acronyms

AAD = average American diet
apo = apolipoprotein
ASCVD = atherosclerotic cardiovascular disease
Low-Sat = low-SFA diet
Lp(a) = lipoprotein(a)
MUFA = monounsaturated fatty acid
NCEP = National Cholesterol Education Program
PUFA = polyunsaturated fatty acid
SFA = saturated fatty acid

well-controlled studies have been carried out in these specific populations.[10,11,16]

Even as the American public has changed its dietary habits and has begun to approach the goal of 30% total fat and no more than 10% SFAs set by the NCEP Step 1 diet,[12] some individuals and groups have already begun campaigns in the lay and scientific communities to reduce further the intake of total and saturated fats. These proposals have raised concerns about the effects these very-low-fat diets will have on plasma lipoproteins. In particular, we wished to address questions focused on effects of additional reductions in SFAs on LDL cholesterol, on potential decreases in HDL cholesterol,[4,17–21] and on lipoprotein(a) concentrations.

Methods

Study Population

Each research center (Columbia University, Pennington Biomedical Research Center, Pennsylvania State University, and University of Minnesota) recruited 25 to 30 healthy, normolipidemic subjects between the ages of 22 and 65 years. Recruitment goals were aimed at achieving a final study population that was composed of 60% women, with equal numbers of premenopausal and postmenopausal women; 30% blacks; and similar numbers of men ≥40 and <40 years of age. Subjects were required to be in good health, taking no medications known to affect plasma lipid levels or thrombotic factors, and available for the entire duration of the study. Mean plasma total cholesterol levels, obtained after a 12- to 14-hour fast on two occasions, had to be between the 25th and 90th percentiles for age, race, and sex.[22] Plasma triglycerides and HDL cholesterol, measured at the last screening visit, had to be below the 90th and above the 10th percentile, respectively.

Protocol

This double-blind study of three diets used a crossover design with three feeding periods. Each subject was randomized to one of six diet sequences (ABC, ACB, BAC, BCA, CAB, or CBA). Each diet period was 8 weeks long, with breaks of 4 to 6 weeks between diet periods. The staff prepared each subject's meal individually, with all items containing fat weighed to the nearest 0.1 g and all other foods weighed to the nearest gram. Subjects ate two meals each weekday (either breakfast and dinner or lunch and dinner, depending on the research center) in a supervised cafeteria setting. All food provided had to be eaten on site at that meal. Subjects were provided with a packaged third meal as well as with snacks. On weekends, all meals except Saturday dinner were packaged and provided at the Friday evening meal. Saturday evening dinner was optionally self-selected according to detailed guidelines for a Step 1 diet provided by the staff. This approach was taken to allow some freedom for the participants while not significantly affecting the overall diet composition during each period; the Step 1 diet was used for all subjects because it was between the extremes of dietary fat used in the study and because we did not want to unblind the subjects. Compliance was assessed by tray checks at meals eaten on site and by self-report on standardized forms for packed meals. Subjects were weighed twice weekly; if needed, adjustments were made in caloric intake to maintain stable body weight. Participants were instructed not to change either smoking (fewer than 10% smoked cigarettes) or exercise habits.

Blood samples were obtained once each week during weeks 5, 6, 7, and 8 of each diet period. This design was chosen to ensure that there was adequate time to achieve steady-state levels of lipids, lipoproteins, and thrombogenic factors. Subjects fasted overnight before blood sampling. Standardized blood sampling and processing procedures were validated and used at all four clinical centers.

Diets

The goal of DELTA-1 was to determine the effects of reducing total fat and SFAs on plasma lipids, lipoproteins, and thrombogenic factors. Three diets were designed: an AAD to provide 37% of calories from fat with 16% SFA, 14% MUFA, and 7% PUFA; a Step 1 diet with 30% of calories from fat and 9% SFA, 14% MUFA, and 7% PUFA; and a low-fat diet with 26% of calories from fat and 5% SFA, 14% MUFA and 7% PUFA fats (hereafter denoted as Low-Sat). The proportions of individual SFAs were designed to be similar in all three diets and to reflect the diet of free-living Americans. To avoid confounding of our results, we maintained *trans*-fatty acids at levels <1.5% of total calories on all three diets. Because our goal was to determine the effects of reducing dietary saturated fat, we designed the diets to provide ≈300 mg/d of dietary cholesterol. Dietary carbohydrate was calculated to be 48%, 55%, and 59% of total calories on the AAD, Step 1, and Low-Sat diets, respectively. All of the diets were designed to provide 15% of calories as protein. The diets were prepared from the same foods with different amounts of various fats and oils added to otherwise low-fat menus, and all the diets were kept isocaloric. All fat sources (meats, margarines, oils, etc) were procured centrally in single lots that were used for the duration of the study. Other foods were specified by brand name and were procured locally. All diets were prepared locally from standardized recipes. An 8-day menu cycle was used during the week and a 4-day cycle on weekends. There was constant diet monitoring during the study in which research centers regularly prepared extra menus (in a blinded fashion) for chemical analyses of homogenates. These analyses were performed by the Food Analysis Laboratory Control Center at Virginia Polytechnic Institute and State University.

Laboratory Tests

All blood samples were collected and processed according to a standardized protocol, and aliquots were stored at −80°C until the end of the study, when all samples were analyzed. Each research center determined serum concentrations of total and HDL cholesterol and triglycerides by use of enzymatic assays. HDL cholesterol was determined after precipitation of apoprotein B–containing lipoproteins with dextran sulfate (MW 50 000). LDL cholesterol levels were calculated [LDL cholesterol=total cholesterol−(HDLC+triglyceride/5)]. The laboratories all participated in a special standardization program with the Centers for Disease Control. The within-laboratory coefficients of variation were ≤1.9% for cholesterol and ≤2.5% for HDL cholesterol. The interlaboratory coefficients of variation were ≤2.8% for cholesterol and ≤6.1% for HDL cholesterol. Measurements of apo B, apo A-I, and Lp(a) were performed at the Mary Imogene Bassett Research Institute. Rate immunonephelometry (Beckman Array) was used to measure apo B and apo A-I;[23] Macra Lp(a) ELISA (Strategic Diagnostics) was used to determine Lp(a) levels.[24] The intra-assay coefficients of variation of the apoprotein assays were <6%. The pattern of each subject's apo E isoforms was determined by polymerase chain reaction using the *Hha*I restriction enzyme.[25]

Statistical Analyses

Effects of reducing dietary SFAs were evaluated in terms of seven serum response variables: cholesterol, LDL cholesterol, HDL cholesterol, triglycerides (natural log scale), apo B, apo A-I, and Lp(a) (square root scale). The statistical computations for longitudinal analysis of the repeated measurements were performed separately for each of these response variables. The linear statistical model, the set of primary hypotheses, the strategy for controlling type I error, and the estimation

TABLE 1. Clinical Characteristics

	Men	Women	Total
No.	46	57	103
Age, y			
Mean	36.0	39.4	37.9
Range	22–65	22–67	22–67
BMI, kg/m^2			
Mean	24.7	24.4	24.5
Range	18.5–30.9	17.3–32.1	17.3–32.1

	Blacks	Nonblacks
No.	26	77
Age, y		
Mean	36.2	38.5
Range	22–67	22–67
BMI, kg/m^2		
Mean	25.3	24.3
Range	18.8–31.5	17.3–32.1

	Premenopausal Women	Postmenopausal Women
No.	39	18
Age, y		
Mean	31.0	57.5
Range	22–51	43–67
BMI, kg/m^2		
Mean	23.8	25.7
Range	17.3–29.8	18.8–32.1

	Men <40 y	Men ≥40 y
No.	30	16
Age, y		
Mean	28.5	50.1
Range	22–39	41–65
BMI, kg/m^2		
Mean	24.5	25.2
Range	18.5–30.7	18.8–30.9

BMI indicates body mass index.
Women were divided by menopausal status.
Men were divided by age <40 or ≥40 years.

procedures were all specified a priori. All statistical tests of significance reported in this article were based on this a priori model. The mean of the conditional distribution of assay values was assumed to be a linear function of six categorical factors: diet (3), race (2), sex-age group (4), apo E genotype (3), research center (4), feeding period (3), and interaction of diet with race, sex-age group, genotype, and field center. The variance of the conditional distribution of assay values was assumed to be constant across all factor levels and occasions. The correlation between any two of an individual's assay values was assumed to be larger for same-diet pairs, smaller for different-diet pairs, but otherwise invariant. This model was represented and interpreted as a components-of-variance model, with the residual variance being a sum of the three components: interindividual variance of the individuals' overall mean levels ("subject"), interindividual variance of the individuals' diet-specific means ("diet-by-subject"), and intraindividual variation ("within-subject").

The study data were used to compute estimates of the regression coefficients and the components of variance. The estimates of components of variance were later used to obtain final power analyses specific to the design, sample size, modeling assumptions, and inferential methods of the study. These computations indicated that the study provided 90% power for detecting a 6.58-mg/dL change in total cholesterol when any two diets were compared via a test procedure of size α=.01. Comparable values for LDL cholesterol, HDL cholesterol, triglycerides, and Lp(a) were 5.45, 2.54, 1.11, and 0.02 mg/dL.

The statistical computations were performed by the mixed-model procedure of the SAS software system.[26] To avoid excess fine-tuning of the model, each term in the regression equation was designated as being either compulsory for inclusion or subject to removal by a backward elimination testing procedure. Any noncompulsory term not significant at the α=.10 level would be dropped before formal testing of the primary hypotheses at the α=.01 level; none were. The primary a priori hypotheses for each of the seven serum responses were as follows: (1) diet effects exist, and these effects are present for (2) blacks, (3) nonblacks, (4) women, (5) men, (6) premenopausal women, (7) postmenopausal women, (8) younger men, and (9) older men.

Results

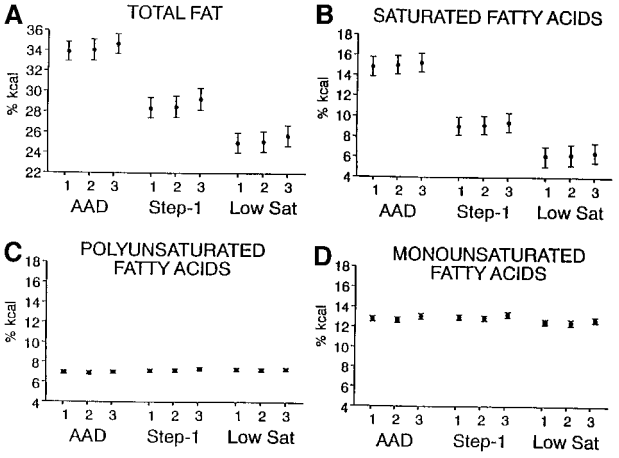
Table 1 presents the clinical characteristics of the subjects. One hundred eighteen subjects were randomized at the start of the study. One hundred three individuals completed the protocol: 55% were women and 45% men. The mean age of the entire group was 37.9 years, with a range from 22 to 67 years. Thirty percent of the women and 20% of the men were black. Thirty-two percent of the women were postmenopausal; 35% of the men were ≥40 years old. Body mass index ranged from 17.3 to 32.1, with a mean of 24.4 for the women and 24.7 for the men. Fifty-five percent of the subjects had the ϵ3/3 genotype, 32% ϵ3/4, 6% ϵ3/2, 3% ϵ2/2, 2% ϵ2/4, and 2% ϵ4/4. The prevalence of apo E genotypes differed by race (data not shown). The association of apo E genotype and diet response was reported separately.[26a]

Table 2 presents the assayed values for the major nutrients in each diet. Palmitic acid (C16:0) was the major SFA, constituting ≈60% of the total saturated fat calories on the three diets and increasing from 51% to 60% to 64% as the diets changed from AAD to Step 1 to Low-Sat. Stearic acid (C18:0) averaged 22% of calories from SFAs, increasing from 18% to 22% to 26% of saturated fat calories across the three diets. Lauric (C12:0) and myristic (C14:0) acids together made up ≈14% of calories from saturated fats, ranging from 24% to 13% to 6% across the three diets. Values from the 1987–1988 Department of Agriculture's Nationwide Food Consumption Survey for the range of saturated fat calories were palmitic, 52% to 57%; stearic, 25% to 29%; and myristic and lauric, 10% to 16%.[27] A more detailed presentation of all diet compositional data will be presented separately.

TABLE 2. Nutrient Levels in Experimental Diets

	AAD Assay*	Step 1 Assay	Low-Sat Assay
Total fat, % kcal	34.3±0.5	28.6±0.2	25.3±0.5
SFA, % kcal	15.0±0.4	9.0±0.1	6.1±0.5
MUFA, % kcal	12.8±0.1	12.9±0.1	12.4±0.1
PUFA, % kcal	6.5±0.1	6.7±0.1	6.7±0.1
Cholesterol, mg/d	285±3.9	267±7.6	275±4.0

*Mean±SEM based on 24 complete menu cycles for AAD, 23 cycles for Step 1, and 22 cycles for Low-Sat.



Results of monitoring each diet (AAD, Step 1, and Low-Sat) during each of the diet periods (1, 2, and 3). Full diet cycles were sampled at each Field Center by each daily menu being collected and frozen individually. Each center's full menu cycle (eight daily samples) was shipped frozen to the Food Analysis Laboratory Control Center, homogenized together, and assayed as a composite. Each value is the mean±SD, as percentage of total kilocalories, of the results of composites from the four field centers. A, Total fat; B, SFAs; C, PUFAs; and D, MUFAs.

Prefeeding validation and continual monitoring of nutrient levels in diets "as prepared and fed" allowed the delivery of virtually identical diets at four separate sites. Monitoring of nutrient composition also demonstrated that the diets met design criteria throughout the study (Figure). There were no between-center differences in diet composition for any diet. The diets were well accepted by the participants, and dietary compliance, as assessed by daily records and interviews, was outstanding at all research centers. During the study, weight fluctuated by <2%.

Table 3 shows the means and SEMs for each of the lipid and apolipoprotein end points during the last 4 weeks of each diet period for all 103 subjects. ANOVA of all end points between weeks 5 and 8 demonstrated stability of means and variance during this period. Analysis of the data demonstrated that essentially identical changes occurred at each research center in association with reductions in dietary saturated fat, a finding consistent with the fact that all centers prepared and delivered the same meals. No significant period effects were observed in this study. On the AAD, the overall group means for total, LDL, and HDL cholesterol levels were approximately the 50th percentile for middle-aged Americans.[22] Total cholesterol decreased ≈5% between the AAD and the Step 1 diet and was reduced an additional 4% during consumption of the Low-Sat diet. The changes in total cholesterol were mirrored by changes in LDL cholesterol, which dropped ≈7% as the subjects went from the AAD to the Step 1 and then fell an additional 4% when they consumed the Low-Sat diet. Decreases in apo B levels were smaller but paralleled the reductions in LDL cholesterol across the three diets. Plasma triglyceride concentrations increased ≈9% between AAD and Step 1 but did not change further when the participants switched to the Low-Sat diet. HDL cholesterol levels fell ≈7% between the AAD and Step 1 diets and dropped an additional 4% during the Low-Sat–diet period. Plasma apo A-I concentrations declined in a parallel fashion. The ratio of total to HDL cholesterol increased ≈2% from AAD to Step 1 and ≈3% from AAD to Low-Sat. Plasma Lp(a) concentrations increased between the AAD and the Step 1 diets and between Step 1 and Low-Sat. Overall, Lp(a) levels increased ≈15% as saturated fat was reduced from 15% to 6% of total calories. The differences in plasma concentrations between AAD and Step 1 were significant ($P<.01$) for all variables except apo B ($P=.013$). Differences between AAD and Low-Sat were all significant except for triglycerides ($P=.054$). Differences between Step 1 and Low-Sat were significant for all values except triglyceride and apo B. None of the changes in the ratio of total to HDL cholesterol were significant.

TABLE 3. Diet Effects on Lipids and Apolipoproteins

	AAD	Step 1	Low-Sat
TC	202.1±2.8*†	191.0±2.7‡	183.4±2.7
LDLC	131.4±2.7*†	122.2±2.6‡	116.9±2.6
HDLC	52.2±1.1*†	48.5±1.1‡	46.2±1.0
TG	85.1±3.4*	92.4±3.7	93.0±3.7
Apo B	116.8±2.4†	113.6±2.6	111.6±2.6
Apo A-I	142.2±2.0*†	135.4±2.0‡	130.4±1.9
Lp(a)	15.5±1.8*†	17.0±1.8‡	18.2±1.9
TC/HDL	4.07±0.10	4.16±0.11	4.21±0.11

TC indicates total cholesterol; LDLC, LDL cholesterol; HDLC, HDL cholesterol; and TG, triglyceride. These values are mean±SEM, for the overall group of 103 subjects. They have been adjusted only for slight period effects observed. The TG values are antilogs of ln(TG) data. The Lp (a) values are squares of square-root data. All values are mg/dL.

*$P<.01$ AAD vs Step 1, based on adjusted values from the linear regression model described in "Methods."

†$P<.01$ AAD vs Low-Sat, based on adjusted values from the linear regression model described in "Methods."

‡$P<.01$ Step 1 vs Low-Sat, based on adjusted values from the linear regression model described in "Methods."

A major goal of DELTA-1 was to determine the effects of reducing dietary SFAs in specific subgroups of the population. The effects of the three diets on plasma lipid levels are therefore depicted separately by sex, race, menopausal status, and age (in the men) in Tables 4A through 4D. With a few exceptions, significant effects ($P<.01$) were observed in each subgroup for all variables when diet was changed from AAD to either Step 1 or Low-Sat. The reductions in total cholesterol on the Step 1 diet compared with the AAD ranged from 4.7% to 5.9% for the different subgroups, with a mean of 5.5%. The differences between AAD and the Low-Sat diet ranged from 7.6% to 10.0%, with a mean of 9.1%. Each diet effect on total cholesterol in each of these groups was significant at $P<.01$.

The differences in plasma LDL cholesterol levels for each of the subgroups on the Step 1 or Low-Sat diets were compared with those on AAD. These results paralleled those for total cholesterol. LDL cholesterol levels decreased ≈7.0% (6.3% to 7.4% for the various subgroups) when subjects changed from the AAD to the Step 1 diet. The average difference between the AAD and the Low-Sat diet was ≈11% (8.8% to 12.4%). Diet effects on LDL cholesterol were significant in all subgroups ($P<.01$). Plasma concentrations of apo B, essentially the only protein in LDL, changed in a similar, albeit more modest, manner as dietary saturated fat was reduced. Significant reductions in apo B levels ($P<.01$) were observed only when the AAD was compared with the Low-Sat diet, although this

TABLE 4A. Diet Effects on Lipids and Apolipoproteins by Sex

	AAD	Step 1	Low-Sat
TC			
Men	202.3±4.1	191.3±4.2*	184.4±3.9*
Women	201.9±3.8	190.7±3.7*	182.7±3.7*
LDLC			
Men	134.4±4.1	125.1±3.9*	120.2±3.8*
Women	128.9±3.5	119.9±3.4*	114.3±3.5*
HDLC			
Men	46.5±1.3	42.8±1.4*	40.6±1.1*
Women	56.2±1.4	52.5±1.3*	50.1±1.3*
TG			
Men	96.5±6%	104.6±6%	107.8±6%
Women	76.7±5%	83.1±5%*	82.3±5%
Apo B			
Men	121.4±3.8	117.6±4.0	116.7±4.0*
Women	113.1±3.0	110.3±3.4	107.5±3.4*
Apo A-I			
Men	132.0±2.4	124.1±2.1*	120.6±1.9*
Women	150.4±2.6	144.6±2.6*	138.4±2.6*
Lp(a)			
Men	11.3±2.0	12.8±2.3*	14.4±2.5*
Women	19.0±2.6	20.3±2.7*	21.5±2.9*
TC/HDL			
Men	4.52±0.17	4.65±0.17	4.71±0.18
Women	3.71±0.11	3.77±0.12	3.80±0.13

Abbreviations and values as in Table 3.

*$P<.01$ either Step 1 or Low-Sat vs AAD, based on adjusted values from the linear regression model described in "Methods."

TABLE 4B. Diet Effects on Lipids and Apolipoproteins by Race

	AAD	Step 1	Low-Sat
TC			
Blacks	195.5±5.4	184.6±4.8*	176.2±4.7*
Nonblacks	204.3±3.2	193.1±3.3*	185.6±3.2*
LDLC			
Blacks	128.1±5.2	119.4±4.8*	113.1±4.7*
Nonblacks	132.4±3.1	123.1±3.0*	118.2±3.1*
HDLC			
Blacks	51.5±2.0	48.3±2.1	46.1±1.8*
Nonblacks	52.0±1.3	48.1±1.2*	45.7±1.2*
TG			
Blacks	71.5±8%	76.7±8%	75.9±9%
Nonblacks	90.0±4%	98.5±4%*	99.5±4%*
Apo B			
Black	112.9±4.4	109.9±4.9	106.4±5.3*
Nonblacks	118.1±2.8	114.8±3.1	113.4±3.0*
Apo A-I			
Blacks	140.3±4.1	135.1±4.2	130.2±4.2*
Nonblacks	142.8±2.3	135.5±2.3*	130.5±2.1*
Lp(a)			
Blacks	24.3±3.6	26.6±3.9*	28.5±4.0*
Nonblacks	12.7±1.8	13.9±1.9*	14.4±2.5*
TC/HDL			
Blacks	3.93±0.18	3.99±0.19	3.97±0.19
Nonblacks	4.12±0.12	4.22±0.13	4.28±0.14

Abbreviations and values as in Table 3.

*$P<.01$ either Step 1 or Low-Sat vs AAD, based on adjusted values from the linear regression model described in "Methods."

comparison was not significant in postmenopausal women or in older men.

Plasma HDL cholesterol concentrations also were lower on the Step 1 and Low-Sat diets than on the AAD ($P<.001$) in all subgroups except blacks (AAD versus Step 1) and older men (AAD versus Step 1). Overall, plasma HDL cholesterol levels decreased by 7.0% (5.9% to 8.6%) when subjects changed from AAD to Step 1. The change from AAD to Low-Sat was associated with a mean reduction of 11.3% (10.0% to 12.9%) in HDL cholesterol concentrations. Plasma levels of apo A-I changed in parallel with levels of HDL cholesterol; significant reductions were observed for all comparisons except AAD versus Step 1 in blacks, postmenopausal women, and older men.

Plasma triglycerides, presented as antilogs of natural log triglycerides, increased significantly in women and nonblacks changing from AAD to Step 1 and in nonblacks changing from AAD to Low-Sat; this increase was ≈10%. In all other subgroups, increases in plasma triglycerides were not statistically significant, ranging from 1% to 12% as dietary fat was reduced. Of interest, there was no further increase in plasma triglyceride between the Step 1 and the Low-Sat diets despite an additional reduction of 4% in total fat and a concomitant further increase in dietary carbohydrate.

Lp(a) levels, depicted as the squares of square roots of plasma concentrations, increased in all subgroups ($P<.01$) except postmenopausal women and older men as dietary saturated fat was reduced from AAD to Step 1. Lp(a) levels increased in all groups as diet changed from AAD to Low-Sat.

Discussion

Ecological,[28–30] immigration,[31,32] and some cohort studies[33–36] have indicated that dietary saturated fat is associated with an increased incidence of ASCVD. One primary[37] and two secondary intervention trials[38,39] demonstrated that reductions in saturated fat and cholesterol are associated with lowered plasma cholesterol concentrations, reduced ASCVD, and improved mortality rates.[40] The NCEP Step 1 diet is the cornerstone of the population-based approach and is the first diet recommended for high-risk individuals.[12] However, few carefully controlled studies have been carried out to demonstrate the efficacy of the Step 1 diet. In studies with large numbers of subjects by Bae et al,[6,7] Denke,[10] and Denke and Grundy,[11] subjects were instructed in the diets but were "free-living." In better-controlled studies,[8,9,13–15] the groups were small. In addition, although women have been included in several diet studies, particularly those by Mensink and colleagues,[41–43] little or no information is available regarding carefully controlled trials of the response to the Step 1 diet in women and in blacks. Even less information is available

TABLE 4C. Diet Effects on Lipids and Apolipoproteins Women by Menopausal Status

	AAD	Step 1	Low-Sat
TC			
Pre	188.7±2.9	177.9±2.8*	169.5±2.6*
Post	230.5±6.2	218.4±6.3*	211.3±6.1*
LDLC			
Pre	116.73±3.0	108.0±2.9*	102.1±2.8*
Post	155.4±5.2	145.4±4.9*	140.7±5.3*
HDLC			
Pre	56.3±1.7	52.9±1.7*	50.2±1.6*
Post	55.8±2.5	51.6±2.3*	49.7±2.2*
TG			
Pre	72.2±5%	78.3±5%	78.3±6%
Post	87.4±9%	95.6±10%	92.8±11%
Apo B			
Pre	104.7±2.8	101.0±3.0	107.5±3.4*
Post	131.3±5.0	130.6±6.5	129.2±6.6
Apo A-I			
Pre	148.3±3.0	142.5±3.0*	135.3±2.8*
Post	155.1±4.9	149.1±5.0	145.3±5.4*
Lp(a)			
Pre	20.2±3.5	21.6±3.7*	22.9±3.9*
Post	16.6±3.6	17.6±3.6	18.74±4.0*
TC/HDL			
Pre	3.47±0.12	3.50±0.13	3.53±0.14
Post	4.23±0.17	4.35±0.21	4.37±0.21

Pre and post indicate premenopausal and postmenopausal, respectively; other abbreviations and values as in Table 3.

*$P<.01$ either Step 1 or Low-Sat vs AAD, based on adjusted values from the linear regression model described in "Methods."

TABLE 4D. Diet Effects on Lipids and Apolipoproteins in Men by Age

	AAD	Step 1	Low-Sat
TC			
<40 y	192.8±4.3	181.6±4.5*	174.5±4.3*
≥40 y	220.2±6.9	209.5±6.5*	202.9±5.7*
LDLC			
<40 y	123.7±4.5	115.5±4.4*	109.5±4.2*
≥40 y	154.5±5.5	143.1±5.4*	140.3±4.7*
HDLC			
<40 y	48.1±1.6	43.8±1.4*	41.7±1.3*
≥40 y	43.5±2.4	40.8±2.8	38.6±2.1*
TG			
<40 y	94.6±8%	100.5±8%	105.6±8%
≥40 y	100.5±10%	114.4±10%	112.2±9%
Apo B			
<40 y	111.6±4.0	107.1±4.1	106.1±4.3*
≥40 y	139.8±5.5	137.4±5.9	136.7±5.6
Apo A-I			
<40 y	134.0±3.3	124.5±2.6*	121.9±2.5*
≥40 y	128.2±3.4	123.2±3.8	118.2±2.9*
Lp(a)			
<40 y	7.9±1.7	9.4±2.0*	10.4±2.2*
≥40 y	19.3±5.2	20.4±5.6	23.3±5.9*
TC/HDL			
<40 y	4.15±0.18	4.26±0.17	4.32±0.18
≥40 y	5.22±0.27	5.38±0.32	5.46±0.30

Abbreviations and values as in Table 3. *$P<.01$ either Step 1 or Low-Sat vs AAD, based on adjusted values from the linear regression model described in "Methods."

concerning the Step 2 or even lower-fat diets recommended for high-risk individuals who do not achieve adequate lowering of their LDL cholesterol level on the Step 1 diet.[18,44,45]

DELTA-1 was designed specifically to define the efficacy of the Step 1 diet and a diet with further reductions in saturated fat in a large number of subjects, including blacks and nonblacks, young and older men, and premenopausal and postmenopausal women. The results presented in this report demonstrate that both the Step 1 and the Low-Sat diets were efficacious in lowering total and LDL cholesterol levels in the entire study group. The reductions we observed were smaller than would have been predicted from the equations of Keys et al[2] and Hegsted et al.[1] Our results are, however, in close agreement with the changes predicted by Mensink and Katan[4] from a meta-analysis of 27 trials in which lipoprotein fractions were determined. The effects predicted by Mensink and Katan were also smaller than those observed by Keys et al. Mensink and Katan stated that in the studies they reviewed, in contrast to the stearic acid–free diets used by Keys et al, the average stearic acid content was 30% of total SFAs. When Mensink and Katan adjusted their data by a factor of 0.7 (assuming that stearic acid did not raise cholesterol), they obtained regression coefficients very close to those of Keys et al. In our diets, stearic acid averaged 22% of the total SFA intake, a value in the range of average American intake.[27] In a recent meta-analysis of 19 diet studies, Yu et al[46] also reported regression coefficients that predicted changes similar to those we observed in the present study. Indeed, those authors predicted that for each increase of 1% of calories from cholesterol-raising fatty acids (C:12, C:14, and C:16), plasma total cholesterol would increase by 2 mg/dL; this is what our results demonstrated.

The majority of previous studies conducted to evaluate the efficacy of the Step 1 diet have included only men. Studies that did include small numbers of women did not analyze the results separately. The study by Boyd et al[47] followed more than 200 women who were taught how to prepare and consume very-low-fat diets; they appear to respond similarly to the men studied by Hegsted et al[1] and Keys et al.[2] More recently, Denke[10,11] studied 50 men and 41 postmenopausal women in separate studies: similar reductions in plasma cholesterol of ≈6% to 8% were observed when the Step 1 diet replaced a 40% fat/16% saturated fat diet. Howard et al[48] compared 33 women against 30 men consuming AADs and a modified Step 1 diet that was high in PUFAs and low in MUFAs. LDL lowering was similar, but HDL fell less in the women. In a small study of the effects of the NCEP Step 2 diet, Lichtenstein et al[45] found no differences in response between

the 8 postmenopausal women and the 7 men they investigated. We found that both the Step 1 and Low-Sat diets were efficacious in women. In the men, we observed decreases in LDL cholesterol of 9.3 and 4.9 mg/dL on the two diets, respectively. Stepwise reductions in LDL cholesterol in the women were 9.1 and 5.5 mg/dL.

No studies have presented separately the responses of total and LDL cholesterol in premenopausal and postmenopausal women to diets low in SFAs. Postmenopausal women have higher LDL cholesterol levels and are at increased risk for ASCVD[12] and therefore are candidates for diet modification. In the present study, on the AAD, the postmenopausal women had total and LDL cholesterol levels of 231 and 155 mg/dL compared with levels of 189 and 117 mg/dL in the premenopausal group. When the postmenopausal women consumed the Step 1 diet, their total and LDL cholesterol levels fell by 5.2% and 6.3%, respectively. These results are similar to those reported by Denke[10] in a study of only postmenopausal women. Total and LDL cholesterol levels were reduced by 5.6% and 7.4% during consumption of the Step 1 diet in our group of premenopausal women. Thus, the premenopausal and postmenopausal women we studied had similar responses to the Step 1 diet. Total and LDL cholesterol were also lowered similarly by the Low-Sat diet compared with the AAD in the premenopausal and postmenopausal women.

There have been almost no controlled studies of the Step 1 diet in whites and blacks. Howard et al[48,49] did not observe a clear racial difference in carefully controlled feeding studies. In DELTA-1 we had adequate statistical power to analyze separately the effects of our diets in the blacks and nonblacks. The blacks in our study had total cholesterol concentrations that were ≈4% lower than the levels in nonblacks on AAD. However, both the Step 1 diet and the Low-Sat diet were efficacious in blacks: total cholesterol fell by 5.4% on the Step 1 diet compared with the AAD; it fell an additional 4.2% on the Low-Sat diet. The nonblack group also had stepwise reductions in total cholesterol of 5.5% and 3.5% on the two lower-fat diets compared with the AAD. LDL cholesterol levels were ≈3% lower in the black group than in the nonblacks. Percent reductions associated with lower SFA intakes, however, were similar in blacks and nonblacks.

In the present study, significant falls in HDL cholesterol and plasma apo A-I concentrations occurred in most of the groups on both the Step 1 and the Low-Sat diets compared with AAD. In general, both the men and the women had sequential reductions in HDL cholesterol of ≈6% to 9% as they went from AAD to Step 1 and then reductions of 3.5% to 5.0% from Step 1 to Low-Sat. These similar responses occurred even though the women had ≈25% greater HDL levels on each diet. Exceptions were observed in the blacks and in the older men, in whom nonsignificant changes in HDL cholesterol and apo A-I levels were observed when these groups switched from AAD to Step 1. This apparent lack of response may be a result of limited statistical power, even in this large study. Both of those groups did have significant reductions in HDL cholesterol going from the AAD to the Low-Sat diet.

Plasma HDL cholesterol concentrations fall when dietary saturated fat is reduced, irrespective of the nutrient used as the replacement; our data are consistent with these observations.[4] Reduction in total dietary fat coupled with increased carbohydrate intake results in the greatest decrease in HDL cholesterol[50] and is associated with both increased fractional clearance and decreased secretion of apo A-I.[51,52] Elevated rates of transfer of HDL cholesterol into an increased plasma pool of triglyceride-rich lipoproteins may also play a role in the fall in HDL levels during consumption of high-carbohydrate diets.[53] Although our patients had very normal triglyceride levels that increased modestly on either the Step 1 or Low-Sat diets versus the AAD, changes in HDL between the AAD and either lower-fat diet correlated with changes in plasma triglyceride concentrations: $r=-.40$, $P<.001$ for changes between AAD and Step 1 and $r=-.45$, $P<.001$ for changes between AAD and Low-Sat. Conversely, the mean HDL cholesterol level fell further as subjects changed from the Step 1 to the Low-Sat diet, although plasma levels of triglycerides did not increase further for the group as a whole.

The implications of these reductions in HDL levels during low-fat diets are a matter of current controversy.[54] Although increases in HDL cholesterol in several intervention trials were found to have a beneficial role on outcome,[12,55] intercultural data indicate that lower HDL cholesterol concentrations in populations consuming low-fat diets are not indicative of increased risk for ASCVD.[12,54,56,57] Despite potential confounders inherent in ecological studies, those data suggest that long-term studies will be required to specifically address the question of effects of diet-induced reductions in HDL cholesterol on cardiovascular risk. The smaller reductions in HDL cholesterol observed when MUFAs or PUFAs are used to replace SFAs (rather than carbohydrate)[4,15,58] suggest that modified Step 1 diets might be beneficial in some individuals in whom replacement of SFAs with carbohydrate produces marked changes in HDL cholesterol and triglyceride concentrations.

Lp(a) is a subclass of LDL that contains apo(a) in addition to apo B. Some, but not all, epidemiological studies[59–62] have indicated increased risk for ASCVD as Lp(a) increases. Since >90% of the variability in Lp(a) levels appears to be genetically determined, it was surprising to find a stepwise increase in Lp(a) levels in most of the groups during consumption of both the Step 1 and the Low-Sat diets. Lp(a) concentrations were not altered by changes in dietary saturated fats or cholesterol in several previous studies (for review, see Reference 63). In contrast, Lp(a) levels did rise in the majority of studies in which *trans*-fatty acids were increased.[42,64,65] In the present study, however, levels of *trans*-fatty acids were very low on all three of our diets. Of note, two recent reports suggested that diets with higher stearic acid content as a percentage of fat calories may increase Lp(a) concentrations[66,67]; as we reduced total saturated fat, the content of stearic acid as a percentage of calories increased. Further studies will be needed to confirm and investigate the mechanisms underlying our finding. In our study, the mean values for all subgroups remained in the "normal" range (<30 mg/dL), and it is difficult to assess the impact that these rising Lp(a) levels would have on risk for ASCVD.

In summary, DELTA-1 has demonstrated clearly that reduction of total fat and SFAs in the diet is accompanied by clinically important reductions in total and LDL cholesterol concentrations[68] in all the groups studied, despite differences in levels of these variables on the AAD. Decreases such as those we have observed should be associated with 10% to 20% reductions in

ASCVD in the population.[3,12] Consumption of the Step 1 and Low-Sat diets was also associated with significant reductions in HDL cholesterol and significant increases in Lp(a) concentrations. Plasma triglycerides rose minimally in our normolipidemic subjects. The impact of these potentially atherogenic changes in response to reducing dietary total and saturated fats must be weighed against the clearly demonstrated benefit of reducing LDL cholesterol levels[12] and the beneficial outcomes of clinical trials in which dietary SFAs were reduced.[37–39,69,70]

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