Dietary Restriction of Saturated Fat and Cholesterol Decreases HDL ApoA-I Secretion

Wanda Vélez-Carrasco, Alice H. Lichtenstein, Francine K. Welty, Zhengling Li, Stefania Lamon-Fava, Gregory G. Dolnikowski, Ernst J. Schaefer

Abstract—We examined the mechanisms responsible for the decrease in HDL cholesterol (HDL-C) levels after the consumption of a diet low in total fat, saturated fat, and cholesterol. Twenty-one subjects with a mean age of 58±12 years were placed on a baseline isocaloric diet (15% protein, 49% carbohydrate, 36% fat, and 150 mg/1000 kcals of cholesterol) and then switched to an NCEP Step 2 diet (15% protein, 60% carbohydrate, 25% fat, and 45 mg/1000 kcals of cholesterol). After 6 or 24 weeks on each diet, subjects received a 15-hour primed-constant infusion of [5,5,5–2 H 3]-L-leucine. HDL apoA-I and apoA-II tracer curves were determined by gas chromatography-mass spectrometry and fitted to a monoexponential equation. Compared with the baseline diet, consumption of the Step 2 diet lowered HDL-C mean levels by 15% (1.03±0.23 to 0.88±0.16 mmol/L, P<0.001), apoA-I by 12% (1.25±0.15 to 1.10±0.13 g/L, P<0.001) and the TC/HDL-C ratio by 5% (0.145±0.04 to 0.137±0.03). No significant changes were observed in apoA-II levels and HDL particle size with diet. HDL apoA-I fractional catabolic rate did not change (0.219±0.052 to 0.220±0.043 pools/day, P=0.91) but HDL apoA-I secretion rate decreased by 8% (12.26±3.07 to 10.84±2.11 mg · kg⁻¹ · day⁻¹, P=0.03) during consumption of the Step 2 diet. There was no effect of diet on apoA-II fractional catabolic rate or secretion rate. Our results indicate that the decrease in HDL-C and apoA-I levels during the isocaloric consumption of a Step 2 diet paralleled the reductions in apoA-I secretion rate. (Arterioscler Thromb Vasc Biol. 1999;19:918-924.)

Key Words: diet ■ HDL ■ apolipoprotein kinetics ■ stable isotopes

Dietary restriction of saturated fat and cholesterol are known to decrease total plasma cholesterol, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) levels in humans.¹⁻⁴ The effect of these diets on HDL-C concentration has created some controversy among scientists because of the beneficial and protective effect of high plasma HDL-C levels on coronary heart disease (CHD) risk.⁵⁻⁸ However, it is important to understand how dietary intervention affects the metabolism of HDL to make effective dietary recommendations aimed at treating and preventing CHD. Kinetic studies have made it possible to elucidate the physiological mechanisms by which dietary fat and cholesterol alter plasma lipoprotein levels.

Few human studies have carefully addressed the question of how diets low in saturated fat and cholesterol content affect the metabolism of HDL (Table 1). Blum et al⁹ studied 3 women after consumption of a very high carbohydrate (80%), low fat (<5g) liquid diet. The authors reported that a 39% increase in total HDL protein fractional catabolic rate accounted for the 38% decrease in plasma HDL-C levels. These results did not reach statistical significance. The effect of a diet high in polyunsaturated fat (polyunsaturated/saturated [P/S]= 4) was studied by Shepherd et al¹⁰ in 4 male subjects. The total fat (40%) and cholesterol content (400 mg/day) was kept constant. Compared with a diet high in saturated fat (P/S=0.25), there was a significant reduction of 33% in HDL-C levels associated with a significant 26% reduction in apoA-I secretion rate on the polyunsaturated fat diet. Nestel et al¹¹ studied 7 men on a vegetarian diet with a mean caloric intake of 26% fat, 60% carbohydrates, 14% protein and <100 mg of cholesterol/day, and 6 men on an average Western diet (36% to 43% fat, 42% to 49% carbohydrate, 15% protein, and 500 to 700 mg of cholesterol/day). The vegetarian subjects had lower levels of HDL-C (~9%) and apoA-I (~18%) and a 59% higher apoA-I fractional catabolic rate compared with the nonvegetarian subjects who served as control. Subsequently, Brinton et al¹² investigated the effects of a low-fat-low cholesterol diet (9% fat, 76% carbohydrate, 16% protein, and 40 mg of cholesterol/1000 kcals) on HDL apoA-I and apoA-II metabolic rates in 13 humans. Compared with a baseline diet (42% fat, 43% carbohydrate, 15% protein and 215 mg of cholesterol/1000 kcals), the authors observed reductions in HDL-C levels and in apoA-I plasma levels of 29% and 23%, respectively. Although there was a significant...
SubjectS
Twenty-one (14 men and 7 women) healthy volunteers underwent a complete physical examination and medical history before admission into the study. The subjects had a mean age of 58 ± 12 years (14 men, mean age 54 ± 12 years, age range 41 to 74 years and 7 women, mean age 66 ± 7 years, age range 53 to 74 years). The subjects had a mean body mass index (BMI) of 27 ± 4 kg/m² (men BMI = 26 ± 2 and women BMI = 27 ± 5). None of the subjects had any evidence of hepatic, cardiac, renal or endocrine dysfunction, or a family history of these illnesses. The subjects did not smoke or consume alcohol regularly and were not taking medications known to alter plasma lipid levels (eg, hydroxymethylglutaryl coenzyme A reductase inhibitors, hormonal preparations, probucol, niacin, fibrin acid derivatives, anion exchange resins, β-blockers, ascorbic acid, fish oil capsules, or thiazide diuretics). All subjects were over 40 years old, and all women were postmenopausal. None of the female participants were on estrogen replacement therapy. The experimental protocol was approved by the Human Investigation Review Committee of the New England Medical Center and Tufts University. All subjects gave informed consent to participate in the study.

Methods

Subjects

Experimental Design

The protocol for this project consists of 2 separate metabolic studies. We studied 11 subjects for 6 weeks on a baseline average American diet followed by a Step 2 diet for 24 weeks. In the second study, both dietary periods lasted for 6 weeks. The length of the Step 2 diet in the second study was reduced to 6 weeks because results from a previous study showed that stabilization of plasma lipid levels occurs by 4 weeks.

The purpose of this study was to examine the effects of a Step 2 diet (<30% fat, <7% saturated fat, and <200 mg of cholesterol per day) on HDL apoA-I and apoA-II kinetics. The Step 2 diet is the diet currently recommended by the American Heart Association and the National Cholesterol Education Program for people with elevated plasma LDL-C levels to treat hypercholesterolemia and prevent CHD. We studied middle-aged and older subjects, who are most likely to have this diet recommended to them. We hypothesized that a Step 2 diet causes a decrease in HDL-C levels due to an increase in apoA-I fractional catabolic rate as well as a decrease in apoA-I secretion rate without an effect on apoA-II metabolic parameters.

The composition of the diets was determined by chemical analysis of food. Values are mean ± SD of 3 preparations of each 3-day meal cycle.

Plasma Lipid and Lipoprotein Determinations

Blood samples were collected in tubes containing 0.15% EDTA and centrifuged at 2500 rpm for 20 minutes at 4°C to separate plasma. Plasma fatty acid composition during each study period was measured by esterification of lipid extracts to monitor adherence to the diets. HDL-C was measured in plasma after precipitation of apoB containing lipoproteins with dextran sulfate-MgCl₂. HDL-C cholesterol was also measured from plasma by a modification of the dextran sulfate-MgCl₂ method. HDL cholesterol concentration represents the difference between HDL-C and LDL-C. Triglyceride rich lipoprotein (TRL, d<1.006 g/mL) and HDL (1.063 to 1.21 g/mL) fractions were obtained by sequential ultracentrifugation (Beckman Instruments Inc) as previously described.

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Quantitation and Isolation of Apolipoproteins

Plasma apoA-I concentration was measured by an immunonutritive assay, using the Spectrum CXX analyzer (Abbott Diagnostics), with reagents and calibrators from Incstar Corp. Plasma apoA-II concentration was assessed by an electroimmunodiffusion technique using commercially available agarose gels with polyclonal apoA-II antibodies incorporated into the gels (Laboratoires Sebia). The coefficients of variation between runs for both measurements were 4% and 10%, respectively. Within each run, the coefficient was approximately 4% for apoA-I and 7% for apoA-II. ApoA-I and apoA-II were isolated from the HDL fraction by SDS polyacrylamide gradient gel electrophoresis using a 6% to 30% acrylamide linear gradient.

The amount of protein loaded was calculated and added to account for the losses during ultracentrifugation. LDL-C was calculated as TC−HDL-C−VLDL-C. All lipid and protein assays were performed in duplicates and the coefficient of variation within and between runs were 2% to 5%.

HDL particle size was determined according to the method of Li et al. Plasma samples were loaded onto nondenaturing polyacrylamide gradient gels (4% to 30%) loaded from Pharmacia, electrophoresed and stained with Sudan black B stain (Fisher). The migration distance of each band was compared with the migration of albumin using a LKB Ultrascan XL laser densitometer (LKB Instruments Inc). A standard curve was obtained using proteins of known sizes and the HDL particle size calculated as the mean diameter of each band multiplied by the fraction of the total area that is occupied by that particular band, expressed as nm.

Isotopic Enrichment Determinations

Polyacrylamide gel bands for apoA-I and apoA-II were cut and subjected to acid hydrolysis with 12N HCL, and incubated at 110°C for 24 hours. Polyacrylamide bands for apoA-I and apoA-II were isolated from the HDL fraction by SDS polyacrylamide gradient gel electrophoresis using a 6% to 30% acrylamide linear gradient. The amount of protein loaded was approximately 100 ug per sample. Protein bands were identified by comparing their migration bands with those of known molecular weight proteins (low molecular weight proteins, Sigma Chemical Co).

Statistical Analyses

The SYSTAT 7.0 software program (SPSS, Inc) was used for all statistical analyses. Paired t tests were used to assess differences between mean values on baseline and Step 2 diets. A linear regression analysis with gender as a covariate was performed to test for correlates of the change in HDL-C levels during the Step 2 diet. For each variable studied, the percent change was calculated.

Results

Plasma Lipids and Apolipoproteins

Plasma lipid and apolipoprotein concentrations during the primed constant infusion are shown in Table 3. All plasma concentrations were measured during the infusion under constant feeding conditions. After consumption of the Step 2 diet, there was a significant decrease in plasma total cholesterol (−19%), LDL-C (−20%), HDL-C (−15%), and apoA-I (−12%) concentrations when compared with the baseline diet. Reductions in HDL2-C (−21%) as well as in HDL3-C (−12%) accounted for the decrease in HDL-C levels with diet. Plasma triglyceride and VLDL-C levels were also lowered during the Step 2 diet and approached statistical significance (−7%, P = 0.058 and −6%, P = 0.051, respectively). This unexpected response may be related to a diminished metabolic responsiveness in this group of older subjects. The Step 2 diet had no effect on plasma apoA-II

<table>
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<tr>
<th>TABLE 3. Effect of a Step 2 Diet on Plasma Lipid, Lipoprotein, and Apolipoprotein Concentrations</th>
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<tr>
<td>Baseline</td>
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<tr>
<td>Total cholesterol (mmol/L)</td>
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<td>VLDL cholesterol (mmol/L)</td>
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<td>ApoA-I (g/L)</td>
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<td>ApoA-II (g/L)</td>
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Lipid values are the mean ± SD of 10 timepoints during the infusion. Apolipoprotein values are the mean ± SD of 4 timepoints during the infusion. *P<0.001, †P<0.05.
Step 2 diet compared with baseline (metabolic rates. The apoA-I pool size decreased 12% on the Step 2 diet, the apoA-I fractional catabolic rate did not change significantly from baseline (4%, \( P=0.91 \)) but the apoA-I secretion rate was significantly lowered (−8%, \( P=0.03 \)). This reduction in apoA-I secretion rate contributed to most of the decrease in plasma apoA-I levels during the Step 2 diet. The mean tracer/tracee ratios for apoA-I and apoA-II during the baseline and Step 2 diet are shown in Figure 1. The apoA-I and apoA-II curves were similar between diets. At 15 hours the maximal apoA-I and apoA-II enrichment curves were about 1% and 0.8%, respectively. Dietary treatment appeared to have little effect on these parameters.

Figure 2 shows the individual variability in dietary response with regard to HDL-C and apoA-I levels, and apoA-I metabolic rates. A decrease in the HDL-C percent change with diet was observed in all but 1 subject, ranging from 2 to −27%. The response in apoA-I levels was more homogeneous (−3% to −22%), but the percent change in apoA-I fractional catabolic rate (45% to −42%) was highly variable, as was the percent change in apoA-I secretion rates (17% to −49%).

With regard to the metabolic rates of apoA-II, we did not observe a significant effect of the Step 2 diet on apoA-II pool size (−2.8%, \( P=0.20 \)), fractional catabolic rate (2.8%, \( P=0.77 \)) or secretion rate (0.20%, \( P=0.46 \)). These results are in agreement with the fact that apoA-II plasma levels remained unchanged after consumption of the Step 2 diet. Within each dietary phase, the apoA-II fractional catabolic rate (baseline, 0.175±0.042; Step 2, 0.171±0.038) was lower than the apoA-I fractional catabolic rate (baseline, 0.219±0.052; Step 2, 0.220±0.043), suggesting that apoA-I is catabolized faster than apoA-II.

Correlates of the Change in HDL-C Levels
A linear regression analysis was performed to examine the relationship between the change in HDL-C levels with diet

Table 5 shows the diet effect on apoA-I and apoA-II kinetic parameters. The mean tracer/tracee ratios for apoA-I and apoA-II during the baseline and Step 2 diet are shown in Figure 1. The apoA-I and apoA-II curves were similar between diets. At 15

| Table 4. Effect of a Step 2 Diet on HDL Composition |
| Baseline | Step 2 |
| Free cholesterol (mmol/L) | 0.195±0.059 | 0.156±0.055† |
| Cholesterol ester (mmol/L) | 0.850±0.166 | 0.707±0.126* |
| Triglyceride (mmol/L) | 0.091±0.027 | 0.090±0.026 |
| Phospholipid (mmol/L) | 0.850±0.160 | 0.723±0.130* |
| Protein (g/L) | 0.060±0.006 | 0.054±0.005* |
| Particle size (nm) | 8.93±0.49 | 8.88±0.52 |
| Pool size (mg) | 4308±759 | 3781±734* |
| SR, mg·kg\(^{-1}\)·day\(^{-1}\) | 12.26±3.07 | 10.84±2.11† |

All values are mean±SD. HDL lipid and protein values were obtained at the 0 hour timepoint during the infusion (n=18). HDL particle size was determined before the beginning of the infusion (n=21). Each value represents the absolute concentration divided by the total mass of the particle and multiplied by 100 (n=18).

*\( P<0.001 \), †\( P<0.01 \), ‡\( P<0.05 \).

concentration. A small but significant reduction in the total cholesterol/HDL-C ratio (−5%, \( P=0.028 \)) was observed after consumption of the Step 2 diet.

HDL Composition
Compositional data for HDL are shown in Table 4. Compared with the baseline diet, HDL unesterified and esterified cholesterol, phospholipids, and protein were significantly lowered (−17%, −16%, −14%, and −9%, respectively) when subjects were switched from a baseline to a Step 2 diet. There was no significant diet effect on HDL triglyceride. The HDL protein effect was mostly due to the diet-associated decrease in apoA-I plasma levels. No significant effect of diet on HDL particle size was noted.

Relative to the total weight of the particle, we observed a modest but statistically significant decrease in the percentage of HDL unesterified cholesterol and an increase in HDL triglycerides on the Step 2 diet compared with baseline. The relative percentages of unesterified HDL cholesterol, phospholipid and protein were not affected by switching from a baseline to Step 2 diet.

HDL ApoA-I and ApoA-II Metabolic Rates
Table 5 shows the diet effect on apoA-I and apoA-II metabolic rates. The apoA-I pool size decreased 12% on the Step 2 diet compared with baseline (\( P<0.0001 \)). During the Step 2 diet, the apoA-I fractional catabolic rate did not change significantly from baseline (4%, \( P=0.91 \)) but the apoA-I secretion rate was significantly lowered (−8%, \( P=0.03 \)). This reduction in apoA-I secretion rate contributed to most of the decrease in plasma apoA-I levels during the Step 2 diet. The mean tracer/tracee ratios for apoA-I and apoA-II during the baseline and Step 2 diet are shown in Figure 1. The apoA-I and apoA-II curves were similar between diets. At 15
and the change in apoA-I and apoA-II metabolic rates. Gender was included in the model as a covariate to adjust for the differences in HDL-C levels between men and women. The change in HDL-C levels correlated with the change in apoA-I ($r = 0.81$, $P < 0.001$), and with the change in triglyceride levels ($r = -0.45$, $P = 0.04$) but not with the change in apoA-II ($r = 0.07$, $P = 0.76$) levels. With regard to apoA-I metabolic rates, the change in HDL-C did not correlate with the change in apoA-I fractional catabolic rate ($r = 0.06$, $P = 0.81$) or with the change in apoA-I secretion rate ($r = 0.30$, $P = 0.19$). In a stepwise multivariate regression analysis, 80% of the variability in HDL-C change with diet was explained by changes in apoA-I, triglyceride levels, and gender.

### Discussion

Our data indicate that switching from a baseline to a Step 2 diet lowers plasma total cholesterol, LDL-C, HDL-C and apoA-I concentrations. We did not observe an increase in VLDL-C and plasma triglyceride levels with the Step 2 diet, commonly seen during the consumption of high carbohydrate diets. One possibility may be that we studied a group of older individuals, who are physiologically less responsive to a carbohydrate-induced hypertriglyceridemia. Another explanation is that the carbohydrate content of these diets was not dramatically increased. In the same group of subjects we have previously reported, no significant difference in fasting triglycerides with an identical diet to that of the current study. However, higher levels of dietary carbohydrate did induce a significant increase in VLDL-C (41%) and triglyceride (47%) levels in similar subjects.

The reduction in apoA-I levels was accompanied by a decrease in apoA-I secretion rates without a significant change in apoA-I fractional catabolic rates. A large degree of individual variability in dietary response with regard to the apoA-I fractional catabolic rates was observed. This variability cannot be attributed to the diet, but probably relates to differences in genetic factors.

The decrease in HDL lipids (with the exception of triglycerides) and protein concentrations without an effect on HDL size suggests a decrease in the number of circulating HDL particles during the Step 2 diet compared with the baseline diet. In addition, the Step 2 diet caused a small alteration in the cholesterol ester and triglyceride content of HDL. Although reductions in both total cholesterol (−19%) and triglyceride (−7%) plasma levels were observed after consumption of the Step 2 diet, the magnitude of the decrease was greater for plasma total cholesterol than for triglycerides. Therefore, it is possible that the higher triglyceride and lower cholesterol ester concentrations in the HDL core of the particle reflects the change in total plasma lipids.

We used a monoexponential equation to analyze the kinetic data with the VLDL apoB100 plateau as an estimate of the apoA-I and apoA-II precursor pool. There are a few limitations associated with using the above parameters to study...
HDL kinetics. The use of a monoexponential equation assumes that the HDL precursor and product pools are homogeneous. With regard to the precursor pool, apoA-I is synthesized in the liver and the intestine whereas apoA-II is only synthesized in the liver. Ikewaki et al reported that the apoA-I fractional catabolic rate obtained with stable isotopes, using a monoexponential function and the VLDL apoB100 plateau, was highly comparable with the one obtained using exogenous radiotracer methods. The closest agreement between stable isotope and radioactive tracer was obtained when 90% of the plasma apoA-I plasma pool was assumed to come from the liver. Although other studies have estimated that up to 50% of circulating plasma apoA-I is synthesized in the intestine, dietary fat and cholesterol do not seem to have an effect on intestinal apoA-I mRNA levels. Therefore it seems appropriate to use the apoB100 plateau as an estimate of apoA-I precursor pool. Moreover, we have recently documented that under constant feeding conditions, TRL apoB100 and apoB48 are catabolized at similar rates and have similar percent enrichment at plateau. With regard to the product pool, it is well established that HDL particles are heterogeneous on the basis of size and protein composition. Previous studies have shown similar enrichment curves for HDL2 and HDL3apoA-I, suggesting a rapid exchange of apoA-I between the two HDL subclasses. With regard to HDL subclasses LpA-I and LpA-I/A-II, Rader and colleagues reported a higher fractional catabolic rates in apoA-I associated with LpA-I compared with apoA-I in LpA-I/A-II particles. However, Tilly-Kiesi et al observed similar apoA-I fractional catabolic rates between LpA-I and LpA-I/A-II subclasses. Although the Step 2 diet did not have an effect on apoA-I fractional catabolic rates in our study, it is possible that a difference in response to the diet exists between apoA-I in LpA-I and apoA-I in LpA-I/A-II. If a difference truly exists, it is of small magnitude because it was not reflected in the total apoA-I fractional catabolic rate change with diet.

In our study, the apoA-I fractional catabolic rates (0.219 ± 0.052 pools/day) and the apoA-II fractional catabolic rates (0.175 ± 0.042 pools/day) were comparable to those obtained using exogenous radioactive tracers at similar levels of dietary fat and cholesterol. Some of these studies used a multiexponential equation, though others used a 2-compartment model to calculate the fractional catabolic rates, and their apoA-I and apoA-II fractional catabolic rates range from 0.228 to 0.242 and 0.186 to 0.200, respectively. Studies conducted in primates and transgenic mice have provided information on the molecular mechanisms by which dietary fat and cholesterol affect HDL-C and apoA-I levels. Sorci-Thomas et al showed that diets high in polyunsaturated fat (P/S ratio = 2.2), at 40% total fat, decrease HDL-C and apoA-I levels by lowering apoA-I mRNA levels and hepatic secretion when compared with a saturated fat diet (P/S = 0.3). This effect was only seen in animals that were fed high levels of dietary cholesterol (0.8 mg/kcal). On the other hand, Brousseau and colleagues reported that replacement of saturated fat with either polyunsaturated or monounsaturated fat without changing the amount of total fat (30%) and dietary cholesterol (0.22 mg/kcal), did not alter apoA-I mRNA abundance and secretion. These results suggest that dietary cholesterol may play an important role in modulating apoA-I secretion rates.

Using a mouse model expressing human apoA-I, Hayek et al observed a decrease in apoA-I fractional catabolic rates and an increase in apoA-I secretion rates in both control and transgenic animals consuming a diet high in total fat (41%) and cholesterol (0.437 mg/kcal) compared with a low fat (9%), low cholesterol (0.057 mg/kcal) diet. There was no significant effect on hepatic apoA-I mRNA levels after the high fat-high cholesterol diet. In addition, increases in HDL cholesterol ester transport rate were also observed in response to an increase in dietary fat and cholesterol. This suggests that the requirement for HDL-mediated cholesterol removal may be less at lower intakes of dietary fat and cholesterol. This response may be compensatory, such that higher secretion rates of apoA-I on an atherogenic diet may be a protective mechanism against the deleterious effects of elevated apoB containing particles on the arterial wall.

Although animal studies have provided valuable information on the regulation of apoA-I gene expression by dietary fat and cholesterol, it remains unclear which dietary factors contribute to the observed changes. In our study, we cannot determine whether the decrease in saturated fat or dietary cholesterol intake accounts for the reductions in apoA-I secretion rates and plasma levels. In addition, the increase in carbohydrate intake to compensate for the decrease in total fat content of the Step 2 diet also may have influenced apoA-I gene expression. However, restriction of dietary saturated fat and cholesterol occurs simultaneously with therapeutic diets designed to lower plasma LDL-C levels. Future studies are needed to evaluate the role of each dietary component on apoA-I gene expression. Such information can be useful in designing diet and/or drug therapies aimed at increasing HDL-C levels and reducing CHD risk.

In summary, we have demonstrated that decreased intakes of total fat, saturated fat and cholesterol as part of Step 2 dietary guidelines beneficially lower total plasma cholesterol and LDL-C levels. Although the Step 2 diet lowers HDL-C plasma levels as well, this should not be viewed as a negative outcome with regard to CHD risk. We observed that the total cholesterol/HDL-C ratio, a strong predictor of CHD, decreased as well. We conclude that consumption of a Step 2 diet is associated with decreases in apoA-I secretion rates.

Acknowledgments

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