Low-fat and high–monounsaturated fatty acid diets decrease plasma cholesterol ester transfer protein concentrations in young, healthy, normolipemic men[1–3]

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ABSTRACT

Background: Cholesterol ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL to apolipoprotein (apo) B–containing lipoproteins. The possible atherogenic role of this protein is controversial. Diet may influence plasma CETP concentrations.

Objective: The objective was to determine whether the changes in plasma lipids observed after consumption of 2 lipid-lowering diets are associated with changes in plasma CETP concentrations.

Design: We studied 41 healthy, normolipidemic men over 3 consecutive 4-wk dietary periods: a saturated fatty acid–rich diet (SFA diet: 38% fat, 20% saturated fat), a National Cholesterol Education Program Step I diet (NCEP Step I diet: 28% fat, 10% saturated fat), and a monounsaturated fatty acid–rich diet (MUFA diet: 38% fat, 22% monounsaturated fat). Cholesterol content (27.5 mg/MJ) was kept constant during the 3 periods. Plasma concentrations of total, LDL, and HDL cholesterol; triacylglycerol; apo A-I and B; and CETP were measured at the end of each dietary period.

Results: Compared with the SFA diet, both lipid-lowering diets significantly decreased plasma total and LDL cholesterol, apo B, and CETP. Only the NCEP Step I diet lowered plasma HDL cholesterol. Positive, significant correlations were found between plasma CETP and total ($r = 0.3868$, $P < 0.0001$) and LDL ($r = 0.4454$, $P < 0.0001$) cholesterol and also between changes in CETP concentrations and those of total ($r = 0.4543$, $P < 0.0001$) and LDL ($r = 0.4554$, $P < 0.0001$) cholesterol.

Conclusions: The isoenergetic substitution of a high–saturated fatty acid diet with an NCEP Step I or a high–monounsaturated fatty acid diet decreases plasma CETP concentrations. *Am J Clin Nutr* 2000;72:36–41.

KEY WORDS Carbohydrates, humans, cholesterol, cholesterol ester transfer protein, CETP, dietary fat, saturated fat, monounsaturated fat, LDL cholesterol, HDL cholesterol, National Cholesterol Education Program Step I diet, Spain, Mediterranean-type diet, men

INTRODUCTION

Cholesterol ester transfer protein (CETP) mediates the transfer of cholesteryl esters and triacylglycerol between HDL and VLDL, IDL, and LDL (1, 2). The possible atherogenic effect of this protein is controversial (3, 4). The plasma CETP concentration, its activity, or both increase in many conditions predisposing to atherosclerosis, such as several types of hyperlipemia (5–9), type 1 diabetes (10), and nephrotic syndrome (11). However, individuals with CETP deficiency have high HDL-cholesterol and apolipoprotein (apo) A-I concentrations (12, 13), conditions associated with a low risk of coronary heart disease. It has been suggested that the increase in plasma CETP concentrations could cause an elevation in plasma LDL-cholesterol concentrations; therefore, high CETP concentrations could be an important atherogenic factor (9, 14).

Several animal studies have shown that the intakes of high-fat and high-cholesterol diets are associated with an increase in plasma CETP concentrations and activities (6, 15–20). In human studies, the intake of saturated fat (21, 22) or *trans* fatty acids (23, 24) increases CETP activity, whereas the intake of oleic acid lowers it (24). To prevent the development of atherosclerosis, current dietary guidelines recommend a reduction in saturated fat intakes. Two approaches to achieve this goal are recommended: *1*) a high-carbohydrate diet, as proposed by the American Expert Panel (National Cholesterol Education Program Step I diet) (25), and *2*) a diet high in monounsaturated fatty acids

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TABLE 1
Energy intake and composition of a food homogenate of the meals fed for 7 consecutive days in each dietary period[1]

	Prediet	SFA diet	NCEP Step I diet	MUFA diet
Protein (% of energy)				
Calculated	17 ± 0.5[2]	15	15	15
Analyzed	—	18.1 ± 0.4	17.6 ± 0.1	17.5 ± 0.2
Fat (% of energy)				
Saturated				
Calculated	16 ± 0.9	20	10	10
Analyzed	—	22.6 ± 0.6	9.2 ± 0.3	9.2 ± 0.2
Monounsaturated				
Calculated	14 ± 0.8	12	12	22
Analyzed	—	10.1 ± 0.3	13.5 ± 0.2	24.4 ± 0.5
Polyunsaturated				
Calculated	6 ± 0.6	6	6	6
Analyzed	—	5 ± 0.2	5.2 ± 0.1	4.8 ± 0.2
Carbohydrates (% of energy)				
Calculated	47 ± 0.9	47	57	47
Analyzed	—	44.2 ± 0.9	54.5 ± 1.1	44.1 ± 0.8
Cholesterol (mg/MJ)				
Calculated	29 ± 1.8	27.5	27.5	27.5
Analyzed	—	26.9 ± 1.2	26.9 ± 1.1	27.9 ± 1
Energy (MJ/d)	10.2	10.2	10.2	10.2

[1] Prediet, diet at the time of enrollment; SFA diet, diet rich in saturated fatty acids; NCEP Step I diet, National Cholesterol Education Program Step I diet (25); MUFA diet, diet rich in monounsaturated fatty acids.
[2] $\bar{x}$ ± SD.

(MUFAs), or a Mediterranean-type diet. The comparative effects of these 2 diets on plasma CETP activity have not been studied. We studied the relative effect of both diets on plasma CETP concentrations and attempted to determine whether the reduction in plasma LDL-cholesterol concentrations induced by these diets is accompanied by changes in CETP concentrations.

SUBJECTS AND METHODS

Subjects

Forty-one white male students aged < 30 y ($\bar{x}$: 20.9 ± 2 y) from the University of Cordoba, Spain, volunteered to participate in the study. All subjects had a comprehensive medical history, physical examination, and clinical chemistry analysis conducted before enrollment. Subjects had total plasma cholesterol concentrations < 5.7 mmol/L (220 mg/dL) while consuming their usual diets. None of the subjects had any chronic illness (eg, hepatic, renal, thyroid, or cardiac dysfunction), had unusually high levels of physical activity, had a family history of coronary artery disease, or used any medication or vitamin supplements in the 6 mo before the start of the study. Physical activity and all food consumed for 1 wk were recorded in a personal log and were used to calculate individual energy requirements. The mean body mass index (BMI; in kg/m^2) of the subjects was 24.5 at the start of the study and remained constant throughout the experimental period. Subjects were encouraged to maintain their usual physical activities and lifestyles and were asked to record in a diary any event that could affect the outcome of the study, such as stress, a change in smoking habits, alcohol intake, or consumption of foods not included in the experimental design. The Human Investigation Review Committee at the Hospital Universitario Reina Sofía approved the study. Informed consent was obtained from all study subjects.

Diets

All subjects consumed 3 diets in succession, each for 28 d. Initially, all subjects consumed a saturated fatty acid (SFA)–rich diet (SFA diet) providing 15% of energy as protein, 47% as carbohydrate, and 38% as fat [20% SFAs, 12% MUFAs, and 6% polyunsaturated fatty acids (PUFAs)]. Next, all subjects consumed a National Cholesterol Education Program Step I diet (NCEP Step I diet) (25) providing 15% of energy as protein, 57% as carbohydrate, and 28% as fat (10% SFAs, 12% MUFAs, and 6% PUFAs). Finally, all subjects consumed an MUFA-rich diet (MUFA diet) providing 15% of energy as protein, 47% as carbohydrate, and 38% as fat (10% SFAs, 22% MUFAs, and 6% PUFAs). Dietary cholesterol was kept constant (27.5 mg/MJ) during the 3 periods. The calculated composition of the diet is shown in **Table 1**.

The compositions of the experimental diets were calculated by using the US Department of Agriculture food tables (26) and Spanish food-composition tables for local foodstuffs (27). Fourteen menus, prepared with regular solid foods, were rotated during the experimental period. Virgin olive oil was used for cooking and salad dressing during the high-MUFA diet; palm oil and butter were used during the SFA diet. Lunch and dinner were consumed in the hospital kitchen. Breakfast and an afternoon snack were prepared by each individual at home according to the recommended foodstuffs and form of preparation. Duplicate samples from each menu were collected, homogenized, and stored at −80 °C. The protein, fat, and carbohydrate contents of the diet were analyzed with standard methods; the results agreed with the calculated composition (Table 1). To assess dietary compliance, fatty acids in LDL cholesteryl esters were determined at the end of each dietary period (28).

Lipid analyses

Venous blood samples were collected into EDTA-containing (1 g/L) tubes from all subjects after a 12-h overnight fast at the

TABLE 2
Fatty acid composition of LDL cholesteryl esters after the 3 dietary periods[1]

Fatty acid	SFA diet	NCEP Step I diet	MUFA diet
		% of total fatty acids	
16:0	26.9 ± 1.4[2]	19.3 ± 3.9	15.2 ± 0.4
16:1	2.1 ± 0.9	2.3 ± 0.3	1.7 ± 0.2
18:0	3.0 ± 1.1	2.3 ± 0.8	2.5 ± 0.4
18:1	46.7 ± 4.4	38.3 ± 9	50.3 ± 4.7[3]
18:2	18.9 ± 3.6	34.9 ± 1.6	29.9 ± 4.8

[1] $\bar{x}$ ± SD; n = 41. SFA diet, diet rich in saturated fatty acids; NCEP Step 1 diet, National Cholesterol Education Program Step I diet (25); MUFA diet, diet rich in monounsaturated fatty acids.
[2] Significantly different from the NCEP Step I and MUFA diets, $P < 0.05$ (ANOVA).
[3] Significantly different from the NCEP Step I diet, $P < 0.05$ (ANOVA).

end of each dietary period. Plasma was obtained by low-speed centrifugation at 789 × *g* for 15 min at 4°C within 1 h of venipuncture. To reduce interassay variation, plasma was stored at −80°C and analyzed at the end of the study in triplicate. Cholesterol and triacylglycerol concentrations were assayed on a Hitachi 704 autoanalyzer with enzymatic kits (Boehringer Mannheim, Mannheim, Germany) (29, 30). HDL cholesterol was measured after precipitation of apo B–containing lipoproteins with phosphotungstic acid (31). Commercially available quality controls (Precinorm and Precilip; Boehringer Mannheim) were included in all the runs. LDL-cholesterol concentrations were calculated from total cholesterol, triacylglycerol, and HDL-cholesterol concentrations with the Friedewald formula (32). Apo A-I and apo B concentrations were determined by turbidimetry (33). The within-run and between-run imprecision of these analytic methods is <3%. CETP was measured by solid-phase immunoassay with TP-2, an anti-human CETP monoclonal antibody, and with recombinant human CETP as a standard (34). The interassay CV was ±6%. Samples were measured in duplicate. A close correlation between plasma CETP mass and in vivo isotopic transfer activity in normal subjects (r = 0.86) and hyperlipoproteinemic subjects (r = 0.72) was shown previously (5).

Statistical analyses

Statistical analyses were carried out by using the CSS statistical package (StatSoft, Inc, Tulsa, OK). We used repeated-measures analysis of variance to test the effects of the diet on plasma lipid concentrations and CETP mass in each dietary phase. When the main significant effects were detected ($P < 0.05$), Tukey's post hoc comparison test was used. All continuous variables, except for triacylglycerol, were normally distributed as assessed by the Kolmogorov-Smirnov test. Triacylglycerol concentrations were logarithmically transformed to achieve approximately normal distribution, and statistical tests were applied to the transformed values. Simple correlation coefficients were used to measure the association between CETP and total and LDL-cholesterol concentrations and between changes in CETP and lipid plasma concentrations after the different diets.

RESULTS

The fatty acid composition of plasma LDL cholesteryl esters after each dietary period is shown in **Table 2**. The amount of palmitic acid (16:0) was significantly higher after the SFA diet than after the NCEP Step I and MUFA diets. Oleic acid (18:1) was significantly higher after the MUFA diet than after the NCEP Step I diet. These differences suggest good dietary compliance.

Plasma lipid and apo A-I and B concentrations before and after each experimental diet period are shown in **Table 3**. Dietary change had a significant effect on plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, apo A-I, and apo B. Total and LDL-cholesterol concentrations were significantly higher after the SFA diet than during the prediet period. Plasma concentrations of the following lipids and apos were significantly lower after the NCEP Step I diet than after the SFA diet by the following amounts: total cholesterol (0.54 mmol/L, or 13%; $P < 0.0001$), LDL cholesterol (0.44 mmol/L, or 17%; $P < 0.0001$), HDL cholesterol (0.1 mmol/L, or 9%; $P < 0.003$), apo A-I (0.1 g/L, or 9%; $P < 0.0001$), and apo B (0.1 g/L, or 17%; $P < 0.0001$). Plasma concentrations of the following lipids and apos were significantly lower after the MUFA diet than after the SFA diet by the following amounts: total cholesterol (0.51 mmol/L, or 12%; $P < 0.0001$), LDL cholesterol (0.42 mmol/L, or 16%; $P < 0.0001$), apo A-I (0.06 g/L, or 5%; $P < 0.0008$), and apo B (0.08 g/L, or 14%; $P < 0.0001$). HDL-cholesterol concentrations were significantly higher after the MUFA diet than after the NCEP Step I diet (0.07 mmol/L, or 7%; $P < 0.014$).

CETP concentrations in each dietary phase are shown in **Figure 1**. CETP concentrations were significantly higher after the SFA diet than after the NCEP Step I and MUFA diets, by

TABLE 3
Plasma lipid and apolipoprotein concentrations at the end of each dietary period[1]

	Prediet	SFA diet	NCEP Step I diet	MUFA diet	P[2]
Total cholesterol (mmol/L)	4.02 ± 0.62[3]	4.24 ± 0.64	3.70 ± 0.59[4]	3.73 ± 0.57[4]	0.0001
Triacylglycerol (mmol/L)	1.01 ± 0.51	1.03 ± 0.42	0.97 ± 0.42	0.87 ± 0.30[4]	0.069
HDL cholesterol (mmol/L)	1.13 ± 0.25	1.19 ± 0.28	1.09 ± 0.23[4]	1.16 ± 0.28[5]	0.007
LDL cholesterol (mmol/L)	2.41 ± 0.52[3]	2.59 ± 0.67	2.15 ± 0.54[4]	2.17 ± 0.59[4]	0.0001
Apolipoprotein A-I (g/L)	1.11 ± 0.19	1.14 ± 0.16	1.04 ± 0.13[4]	1.08 ± 0.15[4]	0.0001
Apolipoprotein B (g/L)	0.57 ± 0.13	0.59 ± 0.15	0.49 ± 0.13[4]	0.51 ± 0.12[4]	0.002

[1] $\bar{x}$ ± SD; n = 41. SFA diet, diet rich in saturated fatty acids; NCEP Step I diet, National Cholesterol Education Program Step I diet (25); MUFA diet, diet rich in monounsaturated fatty acids.
[2] Repeated-measures ANOVA.
[3] Significantly different from the SFA diet, $P < 0.05$.
[4] Significantly different from prediet and SFA diet, $P < 0.05$.
[5] Significantly different from the NCEP Step I diet, $P < 0.05$.

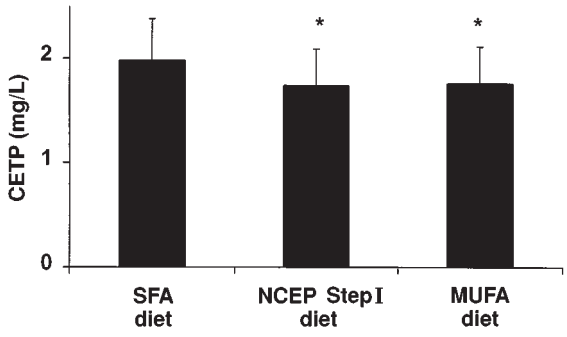

FIGURE 1. Mean (±SD) plasma cholesteryl ester transfer protein (CETP) concentrations in normolipemic men after consumption of a diet rich in saturated fatty acids (SFA diet), a National Cholesterol Education Program Step I diet (NCEP Step I diet) (25), and a diet rich in monounsaturated fatty acids (MUFA diet). *Significantly different from the SFA diet, $P < 0.05$ (ANOVA).

0.24 mg/L (12%) and 0.22 mg/L (11%), respectively. The correlation between plasma concentrations of CETP and those of total cholesterol and LDL cholesterol as well as the changes in plasma CETP, total cholesterol, and LDL-cholesterol concentrations after consumption of the different diets are shown in **Figure 2**. A significant positive correlation was found between CETP and total cholesterol and LDL-cholesterol concentrations. Changes in plasma CETP concentrations were also correlated with those of total and LDL cholesterol.

DISCUSSION

Our data show that the isoenergetic substitution of SFAs with MUFAs or carbohydrates produces a similar, significant decrease in plasma LDL-cholesterol and CETP concentrations. Because of their lipid-lowering effects, both carbohydrate-rich (25) and MUFA-rich diets are recommended for the prevention of atherosclerosis, the latter also having a beneficial effect on plasma HDL-cholesterol concentrations (35–39). In our study, both the NCEP Step I and MUFA diets produced a marked improvement in the lipid profile, lowering plasma total cholesterol and LDL-cholesterol concentrations, and the MUFA diet induced higher concentrations of HDL cholesterol than did the NCEP Step I diet. Our data agree with previous studies that analyzed the effect of MUFA-rich and low-fat diets on HDL-cholesterol concentrations (38, 39).

The observation that CETP concentrations were significantly higher after the SFA diet than after the NCEP Step I and MUFA diets is supported by results of animal studies. In hamsters, a diet enriched with oleic acid lowered plasma CETP activity, whereas a diet high in palmitic acid increased it (20). It was also observed in hamsters that the addition of oleic acid or linoleic acid to a high-cholesterol diet diminished the increases in plasma total

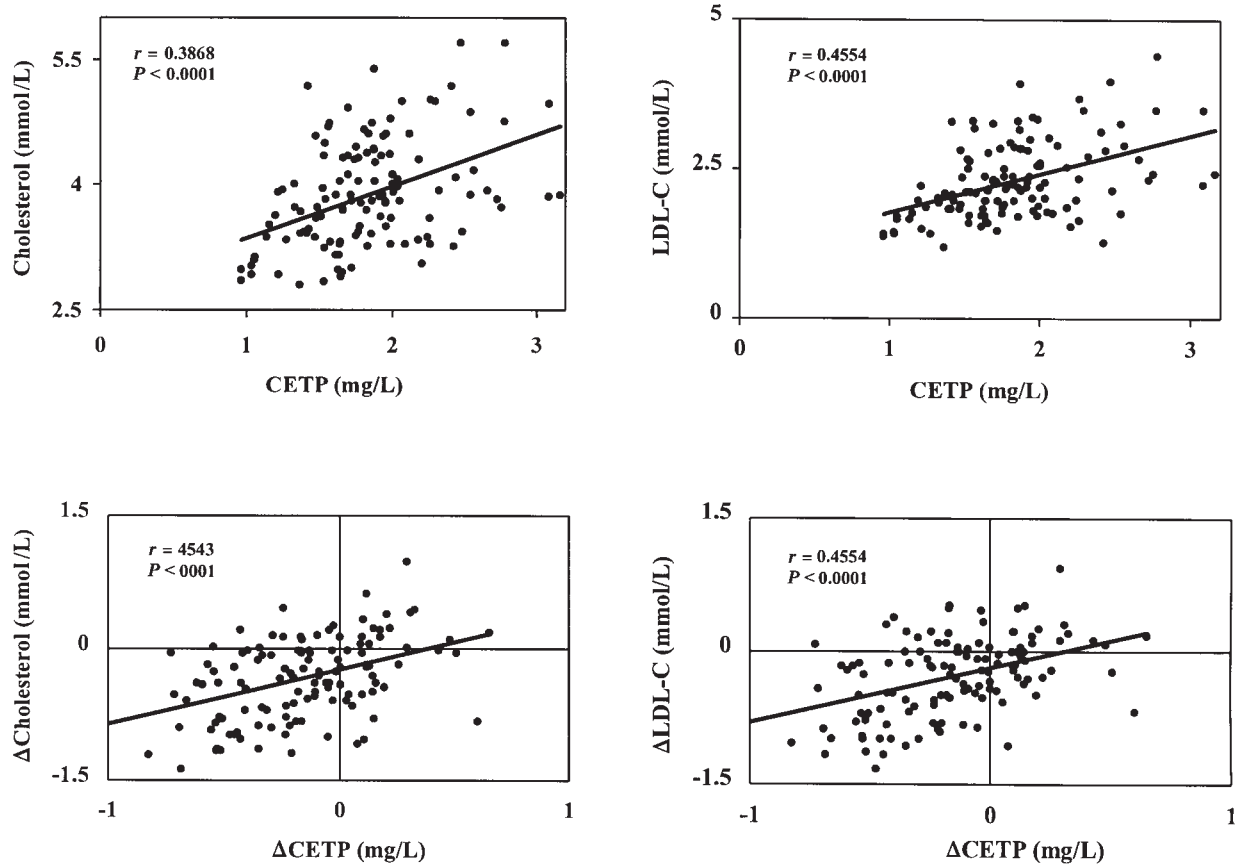

FIGURE 2. Correlation between plasma cholesteryl ester transfer protein (CETP) and total and LDL-cholesterol (LDL-C) concentrations and between changes (Δ) in CETP concentrations and those of total and LDL-C after the 3 different diets.

cholesterol and LDL-cholesterol concentrations induced by cholesterol alone. However, only oleic acid prevents the increase in plasma CETP activity induced by dietary cholesterol while maintaining plasma HDL-cholesterol concentrations (40). A lower plasma CETP activity after the intake of a high-MUFA diet than after the intake of a high-SFA diet was reported in humans (22). In the same study, a correlation between changes in CETP activity and changes in plasma total cholesterol, LDL cholesterol, and (VLDL+LDL) cholesterol was also observed. We studied the effect of a high-MUFA diet on plasma CETP concentrations, comparing it with that of a high-carbohydrate diet. We found a similar decrease in plasma CETP concentrations with both diets and also a correlation between global changes in plasma CETP concentrations and those of total and LDL cholesterol. All MUFAs do not exert the same action on CETP activity. The intake of oleic acid in humans produces a decrease in its activity, whereas the intake of elaidic acid—the *trans* isomer of oleic acid—does not (24). In vitro oleic acid may stimulate or inhibit the transfer of cholesterol esters between HDL_3 and LDL, mediated by CETP depending on the conditions of incubation, whereas elaidic acid raised it under all conditions (41).

The causal relation between changes in CETP and plasma lipid concentrations induced by the diet is not clearly established. Because several conditions associated with hypercholesterolemia also elevate plasma CETP concentrations, it is possible that the activity of this protein may be regulated by plasma cholesterol concentrations. In vitro, the elevation of the intracellular content of cholesterol in human adipose tissue raises CETP messenger RNA concentrations and causes the secretion of CETP (42). Although the extent to which adipose tissue contributes to the plasma CETP pool in humans is not known, it may be partially responsible for the elevated concentrations of CETP associated with certain dyslipemias or with the intake of cholesterol (42). It has been suggested that the combination of dietary SFAs and cholesterol may alter the intracellular cholesterol-regulating pool in hepatocytes (43). It is possible that the lower content of SFAs in NCEP Step I and MUFA-rich diets decreases the intracellular cholesterol content and therefore also decreases CETP secretion in parallel with the fall in plasma LDL-cholesterol concentrations induced by both diets. By contrast, it was shown in rabbits fed a cholesterol-rich diet that the experimental inhibition of CETP activity resulted in lower plasma total cholesterol concentrations and higher HDL-cholesterol concentrations than in rabbits in which no such inhibition was carried out (44). These findings suggest that a decrease in CETP activity may be responsible for changes in plasma cholesterol concentrations. In support of this hypothesis, it was reported that changes in plasma lipids induced by diet in transgenic mice expressing cynomolgus monkey CETP were more prominent than in control animals (45).

Our study showed that both a low-fat diet (NCEP Step I diet) and a Mediterranean-type diet, which is high in MUFAs (MUFA diet), produce similar decreases in plasma CETP concentrations and a reduction in LDL-cholesterol concentrations. The effects of these diets on CETP could be one of the mechanisms by which both diets exert their lipid-lowering and antiatherogenic actions.

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