



HAL
open science

Variations in serum cholesteryl ester transfer and phospholipid transfer activities in healthy women and men consuming diets enriched in lauric, palmitic or oleic acids

Laurent Lagrost, Ronald Mensink, Valérie Guyard-Dangremont, Elisabeth H.M. Temme, Catherine M Desrumaux, Anne Athias, Gerard Hornstra, Philippe Gambert

► To cite this version:

Laurent Lagrost, Ronald Mensink, Valérie Guyard-Dangremont, Elisabeth H.M. Temme, Catherine M Desrumaux, et al.. Variations in serum cholesteryl ester transfer and phospholipid transfer activities in healthy women and men consuming diets enriched in lauric, palmitic or oleic acids. *Atherosclerosis*, 1999, 142 (2), pp.395-402. 10.1016/s0021-9150(98)00244-5 . hal-04207290

HAL Id: hal-04207290

<https://hal.science/hal-04207290v1>

Submitted on 14 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

Variations in serum cholesteryl ester transfer and phospholipid transfer activities in healthy women and men consuming diets enriched in lauric, palmitic or oleic acids

Laurent Lagrost^{a,*}, Ronald P. Mensink^b, Valérie Guyard-Dangremont^a,
Elisabeth H.M. Temme^b, Catherine Desrumaux^a, Anne Athias^a, Gerard Hornstra^b,
Philippe Gambert^a

^a *Laboratoire de Biochimie des Lipoprotéines, INSERM U498, Faculté de Médecine, Hôpital du Bocage, BP 1542, 21034 Dijon, Cedex, France*

^b *Department of Human Biology, Maastricht University, Maastricht, The Netherlands*

Received 13 February 1998; received in revised form 27 July 1998; accepted 17 August 1998

Abstract

Cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) activities were measured in sera from 32 normolipidemic women and men consuming diets enriched in lauric, palmitic, or oleic acids. Serum CETP activity, measured as the rate of radiolabeled cholesteryl esters transferred from HDL toward serum apo B-containing lipoproteins, was higher with the palmitic acid diet ($25.1 \pm 2.5\%$) than with the lauric acid ($23.7 \pm 2.4\%$) and the oleic acid ($24.0 \pm 2.7\%$) diets ($P = 0.0028$ and 0.0283 , respectively). CETP mass concentrations, as measured with an enzyme-linked immunosorbent assay were increased after the lauric acid diet (2.57 ± 0.63 mg/l) and the palmitic acid diet (2.49 ± 0.64 mg/l) as compared with the oleic acid diet (2.34 ± 0.45 mg/l) ($P = 0.0035$ and 0.0249 , respectively). In contrast with CETP, serum PLTP activity, as measured as the rate of radiolabeled phosphatidylcholine transferred from liposomes toward serum HDL, was significantly higher with the lauric acid diet ($23.5 \pm 2.6\%$) than with the palmitic acid diet ($22.5 \pm 2.5\%$) ($P = 0.0013$), while no significant differences were noted when comparing the saturated diets versus the oleic acid diet ($23.0 \pm 2.3\%$). No significant alterations in the mean apparent diameter of LDL, and in the relative proportions of individual HDL subpopulations were observed from one dietary period to another. Nevertheless, lipid transfer activities correlated significantly with the relative abundance of HDL_{2b}, HDL_{2a}, HDL_{3b}, and HDL_{3c}, with opposite tendencies being observed for cholesteryl ester transfer and phospholipid transfer activities. In general, serum CETP activity correlated negatively with HDL cholesterol, but positively with triglyceride concentrations after the dietary interventions, and the relations with serum lipids were just the opposite for PLTP activity. In addition, CETP and PLTP activities correlated negatively when subjects consumed the standardized diets ($P < 0.05$ in all cases), but not when subjects consumed their habitual diet. It is concluded that serum lipid transfer activities in normolipidemic subjects can be significantly affected by the fatty acid content of the diet, with differential effects on CETP and PLTP activities. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Cholesteryl ester transfer protein; Phospholipid transfer protein; Diet; Fatty acid; Plasma; Human

1. Introduction

Several studies have demonstrated that plasma cholesteryl ester transfer protein (CETP) activity can be markedly influenced by the nutrient intake. More specifically, atherogenic high fat/high cholesterol diets were

* Corresponding author. Tel.: +33-3-80-293825; fax: +33-3-80-293661.

associated with an increased transfer of cholesteryl esters from HDL towards plasma apo B-containing lipoproteins, and concordant observations were made in humans [1–3], rabbits [4,5], hamsters [6–8], and baboons [9]. The significant increases in both CETP mRNA levels [5,10] and CETP production rates [11] that were observed in the rabbit after a high cholesterol diet intake came in support of a cholesterol-induced upregulation of CETP gene expression. In addition, CETP expression was shown to be dependent on dietary fatty acid composition. Indeed, plasma CETP levels increase after a diet enriched in saturated or *trans*-unsaturated fatty acids, whereas the enrichment with *cis*-unsaturated fatty acids tends to produce the opposite effect, and concordant observations were made in humans [12–16], marmosets [17], baboons [9], cebus monkeys [18], and hamsters [8]. In addition to their ability to exert a direct effect on CETP levels, dietary fatty acids were also shown to modulate plasma cholesteryl ester transfer rates through alterations in the concentration and composition of plasma lipoprotein substrates, but somewhat contrasting observations could be made by using either CETP mass assays or endogenous lipoprotein-dependent activity assays [16,17,19–21]. In addition, the response of plasma cholesterol to change in dietary fat in humans was shown to be dependent on the baseline plasma CETP activity [22].

In contrast to CETP, the regulation of phospholipid transfer protein (PLTP) activity has only recently been addressed and only fragmentary data are available. The first studies by Meijer et al. [23] found significant rises in CETP and PLTP activities in rabbit plasma in response to cholesterol feeding. When compared with a dairy fat-based diet, a stearic acid-rich diet was recently reported to reduce PLTP activity to a greater extent than did a *trans* fatty acid-rich diet, whereas no concomitant variations in CETP activity were observed [24].

The aim of the present study was to further investigate the role of dietary fatty acids in modulating serum lipid transfer activities *in vivo*. To this end, both CETP and PLTP activities were measured in sera from 32 normolipidemic women and men consuming a diet enriched in either lauric, palmitic, or oleic acids. Effects of these diets on fasting serum lipid and lipoprotein levels have recently been reported [25].

2. Subjects and methods

2.1. Subjects and study design

The study protocol was approved by the ethical committee of Maastricht University, The Netherlands,

and participants gave their written informed consent. Details of study design have been previously described [25]. Briefly, 18 healthy women and 14 healthy men, aged 20–60 years who consumed their habitual diet at the start of the study, completed the trial. Four women and five men were smokers. Study subjects did not take drugs known to affect lipoprotein metabolism, with the exception of two women who took oral contraceptives. Participants were randomly divided into six groups, and they consumed successively three different diets enriched in either lauric acid (44% of total fatty acid intake, weight%), palmitic acid (45% of total fatty acid intake, weight%), or oleic acid (62% of total fatty acid intake, weight%) during three 6-week periods. With the exception of a slightly higher intake of myristic acid (2% of total energy) on the lauric acid diet, nutrient intake was similar in the three diets. The three diets were given in six possible treatment orders and were interrupted by two- to three-week washout periods during which the participants consumed their habitual diets [25].

2.2. Blood sampling

Venous blood samples were collected after an overnight fast in plain glass tubes at the beginning of the study protocol, and at the end of each dietary period. Serum samples were obtained by a 10-min, low speed centrifugation at 4°C, and stored at –80°C until analysis.

2.3. Determination of the size distribution of LDL and HDL by native polyacrylamide gradient gel electrophoresis

Total lipoproteins were ultracentrifugally isolated as the $d < 1.210$ g/ml serum fraction, and they were subsequently separated on 15–250 g/l polyacrylamide gradient gels according to the procedure previously described [26]. The electrophoretic conditions were the same as previously described [27], and gels were stained for proteins with Coomassie brilliant blue G. Finally, the distribution profiles of serum LDL and HDL were obtained by analysis on a BIO-RAD GS-670 imaging densitometer, and apparent diameters of LDL and HDL subfractions were determined by comparison with globular protein standards and latex beads of known diameter. The relative proportions of HDL_{2b} (9.71–12.90 nm), HDL_{2a} (8.77–9.71 nm), HDL_{3a} (8.17–8.77 nm), HDL_{3b} (7.76–8.17 nm), and HDL_{3c} (7.21–7.76 nm) were calculated as the ratio of the corresponding areas under the scan curve to the total area under the entire serum HDL fraction.

Table 1
Lipid and lipoprotein cholesterol concentrations in sera from 32 subjects (18 women, 14 men) consuming diets high in either lauric, palmitic or oleic acid^a

	Lauric acid diet	Palmitic acid diet	Oleic acid diet
Total cholesterol (mmol/l)	5.90 ± 1.02 ^{b,c}	5.69 ± 0.93 ^b	5.42 ± 1.02
LDL cholesterol (mmol/l)	3.84 ± 0.99 ^b	3.71 ± 0.91 ^b	3.49 ± 0.94
HDL cholesterol (mmol/l)	1.59 ± 0.45 ^{b,c}	1.47 ± 0.40	1.44 ± 0.38
Triglycerides (mmol/l)	1.05 ± 0.50	1.11 ± 0.54	1.07 ± 0.42

^a Data (mean ± S.D.) were presented in a previous publication [25].

^b Significantly different from the oleic acid diet, $P < 0.02$.

^c Significantly different from the palmitic acid diet, $P < 0.02$.

2.4. CETP enzyme-linked immunosorbent assay

Serum CETP concentrations were determined by using a competitive ELISA adapted to a Biomek 2000 Laboratory Automation Workstation (Beckman) [28]. CETP mass concentrations were determined in quadruplicate from a calibration curve constructed with a frozen plasma standard [28]. Concentration values were calculated by using the Immunofit EIA/RIA data analysis software (Beckman). The intraassay coefficient of variation was 4%.

2.5. Isotopic assay of cholesteryl ester transfer activity

CETP activity was determined in total serum as the rate of transfer of radiolabeled cholesteryl esters from a tracer dose of ³H-CE-HDL₃ towards serum apo B-containing lipoproteins, as previously described [27]. After incubation of total serum for 3 h at 37°C in the presence of a tracer dose of ³H-CE-HDL₃ and iodoacetate, the mixtures were submitted to an ultracentrifugation step at $d = 1.068$ g/ml, and cholesteryl ester transfer activity was calculated as the percentage of total tritiated cholesteryl esters transferred from the $d > 1.068$ g/ml to the $d < 1.068$ g/ml fractions as compared with control samples kept at 4°C. CETP activity measurements were performed in triplicate. All the serum samples were assayed simultaneously by using the same ³H-CE-HDL₃ preparation, and the intra-assay coefficient of variation of the cholesteryl ester transfer assay was 5%.

2.6. Isotopic assay of phospholipid transfer activity

Serum PLTP activity was determined as the rate of radiolabeled phosphatidylcholine transferred from ¹⁴C-PC-liposomes towards serum HDL according to the procedure previously described [27]. Briefly, total serum was incubated for 30 min at 37°C in the presence of ¹⁴C-PC-liposomes and iodoacetate, and phospholipid liposomes and apo B-containing lipoproteins were precipitated before radioactivity counting [27]. Phospholipid transfer activity was calculated as the percentage

of total radiolabeled phosphatidylcholine transferred from ¹⁴C-PC-liposomes to serum HDL after deduction of values from nonincubated controls [27]. Phospholipid transfer rates were determined simultaneously in all the study samples by using the same ¹⁴C-PC-liposome preparation, and the intra-assay coefficient of variation was 5%.

2.7. Other lipid and lipoprotein analyses

Total cholesterol levels were determined by using an enzymatic kit from Boehringer Mannheim (CHOD-PAP method; Monotest cholesterol). HDL cholesterol levels were determined by using the same enzymatic method after selective precipitation of apo B-containing lipoproteins with the Boehringer phosphotungstic acid/MgCl₂ reagent. LDL cholesterol concentrations were calculated using the Friedewald formula. Triglyceride levels were determined by using an enzymatic kit from Sigma Diagnostics.

2.8. Statistical analysis

Data are expressed as mean ± S.D. Data were analyzed by using the general linear models procedure of the Statistical Analysis System [29]. The Tukey method was used to compare the diets pair-wise, and Pearson correlation coefficients were calculated for the relations between lipid transfer activities and serum lipoprotein parameters.

3. Results

3.1. Effects of diets on serum lipids and lipoproteins

The effects of diets enriched in lauric, palmitic or oleic acids on serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were addressed in a recent publication concerning the same population of 18 women and 14 men [25]. As presented again in Table 1, total cholesterol and LDL cholesterol levels were significantly higher after the lauric acid or palmitic

Table 2

Cholesteryl ester transfer activity in serum from 32 subjects (18 women, 14 men) consuming diets high in either lauric, palmitic or oleic acid

	Lauric acid diet (%)	Palmitic acid diet (%)	Oleic acid diet (%)
All	23.7 ± 2.4 ^b	25.1 ± 2.5 ^c	24.0 ± 2.7
Women	23.5 ± 2.6	24.7 ± 2.7 ^d	22.8 ± 2.5
Men	24.0 ± 2.2 ^a	25.6 ± 2.3	25.5 ± 2.1 ^e

^a Significance of the difference from the palmitic acid diet, $P < 0.03$.

^b Significance of the difference from the palmitic acid diet, $P < 0.005$.

^c Significance of the difference from the oleic acid diet, $P < 0.03$.

^d Significance of the difference from the oleic acid diet, $P < 0.005$.

^e Significance of the difference from women, $P < 0.005$.

acid diets than after the oleic acid diet. HDL cholesterol concentrations were significantly higher with the lauric acid diet as compared with either the palmitic acid diet or the oleic acid diet. No significant differences in HDL cholesterol levels were observed after the palmitic acid diet and the oleic acid diet (Table 1). The triglyceride levels did not differ significantly between the three diets (Table 1). Similar responses to the diets were observed in women and men [25].

3.2. Effects of diets on serum cholesteryl ester transfer activity

As shown in Table 2, cholesteryl ester transfer activity in total serum was higher with the palmitic acid diet than with the lauric acid and the oleic acid diets ($P = 0.0028$ and 0.0283 , respectively). Somewhat different observations were made among women and men, and cholesteryl ester transfer activity was significantly higher in men than in women after the oleic acid diet ($P = 0.0031$).

Serum CETP mass concentrations are given in Table 3. Mean CETP concentrations were increased after the lauric acid and palmitic acid diets as compared with the oleic acid diet ($P = 0.0035$ and 0.0249 , respectively). Similar observations were made in women and men,

Table 3

Cholesteryl ester transfer protein (CETP) mass concentration in serum from 32 subjects (18 women, 14 men) consuming diets high in lauric, palmitic or oleic acid

	Lauric acid diet (mg/l)	Palmitic acid diet (mg/l)	Oleic acid diet (mg/l)
All	2.57 ± 0.63 ^c	2.49 ± 0.64 ^a	2.34 ± 0.45
Women	2.59 ± 0.54 ^b	2.57 ± 0.63 ^b	2.37 ± 0.46
Men	2.54 ± 0.76	2.39 ± 0.66	2.31 ± 0.46

^a Significance of the difference from the oleic acid diet, $P < 0.03$.

^b Significance of the difference from the oleic acid diet, $P < 0.02$.

^c Significance of the difference from the oleic acid diet, $P < 0.005$.

Table 4

Phospholipid transfer activity in serum from 32 subjects (18 women, 14 men) consuming diets high in lauric, palmitic or oleic acid

	Lauric acid (%)	Palmitic acid (%)	Oleic acid (%)
All	23.5 ± 2.6 ^a	22.5 ± 2.5	23.0 ± 2.3
Women	24.0 ± 2.6	23.1 ± 2.3	23.4 ± 2.7
Men	22.8 ± 2.7 ^a	21.8 ± 2.6	22.5 ± 1.7

^a Significantly different from the palmitic acid diet, $P < 0.005$.

although differences did not reach the statistical significance in men.

3.3. Effects of diets on serum phospholipid transfer activity

As shown in Table 4, phospholipid transfer activity in total serum was significantly higher with the lauric acid diet than with the palmitic acid diet ($P = 0.0013$), while no significant differences were noted when comparing the saturated versus the monounsaturated diets. Consistent observations were made with women and men, although the difference between the lauric acid and palmitic acid diets reached the significance level only in men.

3.4. Relations between lipid transfer activities and serum lipoprotein parameters

Serum HDL cholesterol levels correlated negatively with cholesteryl ester transfer activity, but positively with phospholipid transfer activity, and consistent observations were made with all diets (Table 5). In contrast to HDL cholesterol levels, triglyceride levels tended to correlate positively with cholesteryl ester transfer activity, but negatively with phospholipid transfer activity (Table 5). No significant relationships between lipid transfer activities and total cholesterol or LDL cholesterol levels were observed.

No significant alterations in the mean size of LDL were observed among the whole population with any diet, and no significant relationships between LDL size

Table 5
Correlations between lipid transfer activities and lipoprotein parameters in serum from 32 subjects consuming diets high in lauric, palmitic or oleic acid^a

	Cholesteryl ester transfer activity			Phospholipid transfer activity		
	Lauric acid	Palmitic acid	Oleic acid	Lauric acid	Palmitic acid	Oleic acid
Lipid parameters						
HDL cholesterol	-0.44 ^b	-0.46 ^c	-0.66 ^d	0.72 ^d	0.74 ^d	0.68 ^d
Triglycerides	0.36 ^b	0.25	0.38 ^b	-0.45 ^b	-0.43 ^b	-0.32
HDL subfractions						
HDL _{2b}	-0.49 ^b	-0.50 ^c	-0.47 ^c	0.59 ^d	0.57 ^d	0.54 ^c
HDL _{2a}	-0.41 ^b	-0.52 ^c	-0.57 ^d	0.49 ^c	0.47 ^c	0.33
HDL _{3a}	0.05	-0.15	-0.03	-0.09	0.13	-0.22
HDL _{3b}	0.48 ^c	0.56 ^c	0.48	-0.64 ^d	-0.62 ^d	-0.48
HDL _{3c}	0.43 ^b	0.55 ^c	0.62 ^d	-0.36	-0.49 ^c	-0.39 ^b

^a Lipid transfer activities and lipoprotein parameters were determined as described in Section 2.

^b $P < 0.05$.

^c $P < 0.01$.

^d $P < 0.001$.

and lipid transfer activities were noted. The relative proportions of individual HDL subpopulations did not differ significantly from one dietary period to another. Nevertheless, lipid transfer activities correlated significantly with the relative abundance of HDL_{2b}, HDL_{2a}, HDL_{3b}, and HDL_{3c}, and opposite tendencies were observed for cholesteryl ester transfer and phospholipid transfer activities. Thus, at the end of each fatty acid-specific dietary period, cholesteryl ester transfer activity correlated negatively with HDL_{2b} and HDL_{2a}, but positively with HDL_{3b} and HDL_{3c} (Table 5). Conversely, phospholipid transfer activity correlated positively with HDL_{2b} and HDL_{2a}, but negatively with HDL_{3b} and HDL_{3c} (Table 5). Consistent observations were made when subjects entered the trial with their habitual diet.

3.5. Relations between cholesteryl ester transfer activity and phospholipid transfer activity

As shown in Fig. 1, CETP and PLTP activities correlated negatively when subjects consumed the standardized lauric acid diet ($r = -0.39$, $P = 0.0284$), palmitic acid diet ($r = -0.45$, $P = 0.0106$) or oleic acid diet ($r = -0.39$, $P = 0.0287$), but not when subjects consumed their habitual diet ($r = 0.01$, $P = 0.9631$).

4. Discussion

In addition to significant alterations in serum lipid and lipoprotein concentrations [25], the substitution of one fatty acid for another in experimental diets was shown in the present study to induce significant changes in serum CETP activity, and greater cholesteryl ester transfer rates were observed with the palmitic acid diet than with the lauric acid diet and the oleic acid diet.

These results indicated that saturated and monounsaturated fatty acids are able to modify plasma CETP activity, extending previous evidences for alterations in lipid transfer activity in subjects consuming either saturated, *cis*-unsaturated, or *trans*-unsaturated fats [14,16–21]. Significant variations in CETP mass concentrations were also observed in the present study, and the lauric acid diet promoted a significant rise in serum CETP mass concentration as compared with the oleic acid diet. Similar tendencies were reported by Kuroshima et al. [8] when evaluating CETP mass levels by measuring CETP activity in lipoprotein-deficient plasma from hamsters fed either an oleic acid-rich diet or a palmitic acid-rich diet. In contrast, no significant differences in CETP mass levels were noted in the present study after the lauric and palmitic acid diets, an observation that agrees with the absence of differences in mean cholesteryl ester transfer rates measured in lipoprotein-deficient plasma from women consuming diets enriched with either palm oil or coconut oil [13]. Overall, discordance appeared when comparing CETP mass and transfer activity values from the present study. For instance, the lauric acid diet promoted a significant rise in serum CETP mass concentration, but not in serum cholesteryl ester transfer rates as compared with the oleic acid diet. In addition, serum cholesteryl ester transfer rates, but not CETP mass levels were significantly lower after the lauric acid diet than after the palmitic acid diet. The latter observations, together with previous observations from other groups [16,17], confirm that the conclusions drawn when investigating the effect of dietary intervention on CETP activity can vary owing to the experimental approach used, and they indicate that not only CETP mass but also endogenous serum modulators constitute key determinants of the cholesteryl ester transfer pro-

cess. Recent studies on the plasma kinetics of CETP demonstrated that variations in plasma CETP mass induced by dietary manipulations in the rabbit are mainly linked to variations in CETP production rates reflecting CETP gene expression [11]. Based on these

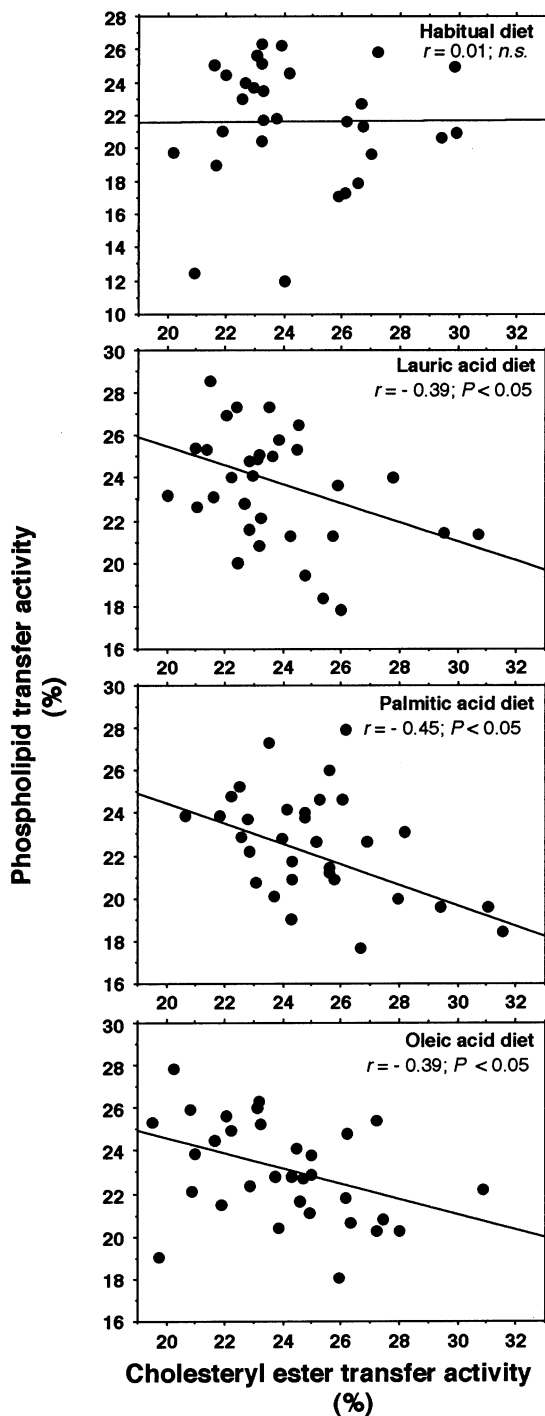


Fig. 1. Correlations of serum phospholipid transfer activity with serum cholesteryl ester transfer activity. CETP and PLTP activities were measured in total sera and expressed as percentage of total radioactivity transferred from the particle donor to the acceptor lipoprotein fraction. The normolipidemic subjects consumed their habitual diet, lauric, palmitic, or the oleic acid diet as indicated.

data, the lower CETP mass levels observed in the present study after the oleic acid diet suggest that CETP gene expression is significantly reduced as compared with the two saturated diets. Although the measurement of cholesteryl ester transfer rates in total serum clearly revealed that CETP mass is not the sole determinant of serum cholesteryl ester transfer activity, endogenous modulators accounting for the diet-induced alterations in the activity of plasma CETP remain to be identified. As proposed in previous trials, variations in CETP activity might relate to variations in the lipoprotein levels and composition, as well as to differences in the transferability of cholesteryl ester molecular species [30,31] that is known to vary according to the fatty acid composition of the diet [32]. In fact, the ability of CETP to transfer cholesteryl ester molecules was shown to be dependent on the nature of the acyl group that might influence either the affinity of cholesteryl esters for CETP or the physical state of the lipoprotein core [30,31,33].

Not only CETP activity, but also PLTP activity was observed to vary significantly from one dietary period to another in the present work. More specifically, phospholipid transfer rates measured in total serum were significantly higher after the lauric acid diet than after the palmitic acid diet. In spite of the lack of a direct quantitation of PLTP mass, the determination of serum PLTP activity in the present study demonstrated that not only the dietary intake of cholesterol [23,34] and of saturated versus *trans*-unsaturated fatty acids [24], but also the chain length of dietary saturated fatty acids can significantly modulate phospholipid transfer rates. Whether dietary fatty acid-induced variations in serum phospholipid transfer activity relate to variations in PLTP gene expression [34], to specificity of PLTP for various phospholipid species [35–37], or to other specific alterations in the serum lipoproteins deserves further investigation.

The present comparative study of serum lipid transfer activities revealed that different diets can produce opposite effects on CETP and PLTP activities as measured in total serum samples. In particular, substituting palmitic acid for lauric acid in the experimental diet was associated with a significant increase in serum CETP activity, but a significant decrease in PLTP activity. Simultaneous evaluation of serum CETP and PLTP activities in dietary studies was conducted only recently, and one study indicated that phospholipid transfer activity, but not cholesteryl ester transfer activity can be significantly affected by the saturated versus the *trans* unsaturated fatty acid content of the diet [24]. Some differences in variations of plasma CETP and PLTP activities were also reported among rabbit strains consuming a high cholesterol diet [23]. In the present study, significant negative correlations between CETP and PLTP activities were noted when subjects con-

sumed one given standardized diet, but not when subjects consumed their habitual diet. Although the occurrence of only transient alterations in lipid transfer activities cannot be definitely excluded after 6-week dietary periods, the results of correlation analysis indicate that a differential regulation of serum CETP and PLTP activities may be unmasked when the nutritional intake is standardized. Unlike PLTP activity, CETP activity was shown to be modulated by non-esterified fatty acids [38], an effect that is dependent on the length and the degree of unsaturation of the acyl chains [39]. The latter point might well account, at least in part for the differential effects of specific diets on plasma PLTP and CETP activities in the present study.

It is now clearly established that CETP and PLTP can modulate the size distribution of serum lipoprotein fractions. On the one hand, CETP can replace lipoprotein cholesteryl esters by hydrolyzable triglycerides which are derived from the triglyceride-rich lipoproteins, favoring the emergence of small-sized LDL, pre β -HDL and small-sized α HDL [40]. On the other hand, PLTP has been shown to promote the formation of both pre β -HDL and large-sized α HDL through an inter-HDL fusional mechanism [40]. In the present study, no significant differences in the size distribution of either HDL or LDL fractions were observed in sera from subjects consuming either of the three experimental diets. In fact, it must be noted that the substitution of one fatty acid for another was associated in the present study with only moderate, however significant variations in serum lipid transfer activities, suggesting that more drastic changes in lipid transfers are required to result secondarily in significant alterations in the size distribution of lipoproteins. Despite the absence of modifications of the size distribution of HDL, significant relationships between lipid transfer activities and the relative abundance of HDL subpopulations were observed among subjects consuming the same, standardized diet. Overall, CETP correlated positively with small HDL, but negatively with large HDL, whereas opposite tendencies were observed with PLTP that correlated negatively with small HDL, but positively with the large ones.

In conclusion, the present study demonstrated that serum lipid transfer activities in normolipidemic subjects can be significantly affected by the fatty acid content of the diet, and differential effects on CETP and PLTP activities were observed. The regulation of the expression of lipid transfer protein genes was only recently addressed, and the molecular mechanisms of the dietary fatty acid-induced regulation of serum CETP and PLTP mass levels deserve further investigation.

Acknowledgements

The technical assistance of Dominique DeBaudus, Elisabeth Niot, and Liliane Princep is greatly acknowledged. The study was supported by grants from the Dutch Dairy Foundation on Nutrition and Health, the Université de Bourgogne, the Conseil Régional de Bourgogne, and the Institut National de la Santé et de la Recherche Médicale (INSERM).

References

- [1] Castro GR, Fielding CJ. Effects of postprandial lipemia on plasma cholesterol metabolism. *J Clin Invest* 1985;75:874–82.
- [2] Tall A, Sammett D, Granot E. Mechanisms of enhanced cholesteryl ester transfer from high density lipoproteins to apolipoprotein B-containing lipoproteins during alimentary lipemia. *J Clin Invest* 1986;77:1163–72.
- [3] Martin LJ, Connelly PW, Nancoo D, Wood N, Zhang ZJ, Maguire G, Quinet E, Tall AR, Marcel YL, McPherson R. Cholesteryl ester transfer protein and high density lipoprotein responses to cholesterol feeding in men: relationship to apolipoprotein E genotype. *J Lipid Res* 1993;34:437–46.
- [4] Quig DW, Zilversmit DB. Plasma lipid transfer activity in rabbits: effects of dietary hyperlipidemias. *Atherosclerosis* 1988;70:263–71.
- [5] Quinet EM, Agellon LB, Kroon PA, Marcel YL, Lee YC, Whitlock ME, Tall AR. Atherogenic diet increases cholesteryl ester transfer protein messenger mRNA levels in rabbit liver. *J Clin Invest* 1990;85:357–63.
- [6] Stein Y, Dabach Y, Hollander G, Stein O. Cholesteryl ester transfer activity in hamster plasma: increase by fat and cholesterol rich diets. *Biochim Biophys Acta* 1990;1042:138–41.
- [7] Shen GX, Angel A. Regulation of cholesteryl ester transfer activity in adipose tissue: comparison between hamster and rat species. *Am J Physiol* 1995;269:99–107.
- [8] Kurushima H, Hayashi K, Shingu T, Kuga Y, Ohtani H, Okura Y, Tanaka K, Yasunobu Y, Nomura K, Kajiyama G. Opposite effects on cholesterol metabolism and their mechanisms induced by dietary oleic acid and palmitic acid in hamsters. *Biochim Biophys Acta* 1995;1258:251–6.
- [9] Kushwaha RS, Reardon CA, Lewis DS, Qi Y, Rice KS, Getz GS, Carey KD, McGill HC Jr. Effect of dietary lipids on plasma activity and hepatic mRNA levels of cholesteryl ester transfer protein in high- and low-responding baboons (*Papio* species). *Metabolism* 1994;43:1006–12.
- [10] Warren RJ, Ebert DL, Barter PJ, Mitchell A. The regulation of hepatic lipase and cholesteryl ester transfer protein activity in the cholesterol fed rabbit. *Biochim Biophys Acta* 1991;1086:354–8.
- [11] McPherson R, Lau P, Kussie P, Barrett H, Tall AR. Plasma kinetics of cholesteryl ester transfer protein in the rabbit. Effects of dietary cholesterol. *Arterioscler Thromb Vasc Biol* 1997;17:203–10.
- [12] Groener JEM, van Ramshorst EM, Katan MB, Mensink RP, van Tol A. Diet-induced alteration in the activity of plasma lipid transfer protein in normolipidemic human subjects. *Atherosclerosis* 1991;87:221–6.
- [13] Schwab US, Niskanen LK, Maliranta HM, Savolainen MJ, Kesäniemi A, Uusitupa MIJ. Lauric and palmitic acid-enriched diets have minimal impact on serum lipid and lipoprotein concentrations and glucose metabolism in healthy young women. *J Nutr* 1995;125:466–73.

- [14] Schwab US, Maliranta HM, Sarkkinen ES, Savolainen MJ, Kesäniemi YA, Uusitupa MIJ. Different effects of palmitic and stearic acid-enriched diets on serum lipids and lipoproteins and plasma cholesteryl ester transfer protein activity in healthy young women. *Metabolism* 1996;45:143–9.
- [15] van Tol A, Zock PL, van Gent T, Scheek LM, Katan MB. Dietary *trans* fatty acids increase serum cholesteryl ester transfer protein activity in man. *Atherosclerosis* 1995;115:129–34.
- [16] Abbey M, Nestel PJ. Plasma cholesteryl ester transfer protein activity is increased when *trans*-elaidic acid is substituted for *cis*-oleic acid in the diet. *Atherosclerosis* 1994;106:99–107.
- [17] Abbey M, Clifton PM, McMurchie EJ, McIntosh GH, Nestel PJ. Effect of a high fat/cholesterol diet with or without eicosapentaenoic acid on plasma lipids, lipoproteins and lipid transfer protein activity in the marmoset. *Atherosclerosis* 1990;81:163–74.
- [18] Khosla P, Hajri T, Pronczuk A, Hayes KC. Replacing dietary palmitic acid with elaidic acid (*t*-C18:1 Δ 9) depresses HDL and increases CETP activity in Cebus monkeys. *J Nutr* 1997;127:531–6.
- [19] Abbey M, Clifton P, Kestin M, Belling B, Nestel P. Effect of fish oil on lipoproteins, lecithin:cholesterol acyltransferase, and lipid transfer protein activity in humans. *Arteriosclerosis* 1990;10:85–94.
- [20] Bagdade JD, Ritter MC, Davidson M, Subbaiah PV. Effect of marine lipids on cholesteryl ester transfer and lipoprotein composition in patients with hypercholesterolemia. *Arterioscler Thromb* 1992;12:1146–52.
- [21] Sugano M, Makino N, Yanaga T. Effect of dietary omega-3 eicosapentaenoic acid supplements on cholesteryl ester transfer from HDL in cholesterol-fed rabbits. *Biochim Biophys Acta* 1997;1346:17–24.
- [22] Cox C, Mann J, Sutherland W, Ball M. Individual variation in plasma cholesterol response to dietary saturated fat. *Br Med J* 1995;311:1260–4.
- [23] Meijer GW, Demacker PNM, van Tol A, Groener JEM, van der Palen JGP, Stalenhoef AFH, van Zutphen LMF, Beynen AC. Plasma activities of lecithin:cholesterol acyltransferase, lipid transfer proteins and post-heparin lipases in inbred strains of rabbits hypo- or hyper-responsive to dietary cholesterol. *Biochem J* 1993;293:729–34.
- [24] Aro A, Jauhainen M, Partanen R, Salminen I, Mutanen M. Stearic acid, *trans* fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr* 1997;65:1419–26.
- [25] Temme EHM, Mensink RP, Hornstra G. Comparison of the effects of diets enriched in lauric, palmitic, or oleic acids on serum lipids and lipoproteins in healthy women and men. *Am J Clin Nutr* 1996;63:897–903.
- [26] Blanche PJ, Gong EL, Forte TM, Nichols AV. Characterization of human high-density lipoproteins by gradient gel electrophoresis. *Biochim Biophys Acta* 1981;665:408–19.
- [27] Lagrost L, Athias A, Herbeth B, Guyard-Dangremont V, Artur Y, Paille F, Gambert P, Lallemand C. Opposite effects of cholesteryl ester transfer protein and phospholipid transfer protein on the size distribution of plasma high density lipoproteins. Physiological relevance in alcoholic patients. *J Biol Chem* 1996;271:19058–65.
- [28] Guyard-Dangremont V, Lagrost L, Gambert P, Lallemand C. Competitive enzyme-linked immunosorbent assay of the human cholesteryl ester transfer protein (CETP). *Clin Chim Acta* 1994;231:147–60.
- [29] SAS Institute. SAS: user's guide to statistics. Version 5. In: Cary, N.C., editor, SAS Institute, 1985.
- [30] Morton RE. Specificity of lipid transfer protein for molecular species of cholesteryl ester. *J Lipid Res* 1986;27:523–9.
- [31] Green SR, Pittman RC. Comparative acyl specificities for transfer and selective uptake of high density lipoprotein cholesteryl esters. *J Lipid Res* 1991;32:457–67.
- [32] Zock PL, Mensink RP, Harryvan J, de Vries JHM, Katan MB. Fatty acids in serum cholesteryl esters as quantitative biomarkers of dietary intake in humans. *Am J Epidemiol* 1997;145:1114–22.
- [33] Morton RE, Parks JS. Plasma cholesteryl ester transfer activity is modulated by the phase transition of the lipoprotein core. *J Lipid Res* 1996;37:1915–23.
- [34] Jiang XC, Bruce C. Regulation of murine plasma phospholipid transfer protein activity and mRNA levels by lipopolysaccharide and high cholesterol diet. *J Biol Chem* 1995;270:17133–8.
- [35] Massey JB, Hickson-Bick D, Via DP, Gotto AM, Pownall HJ. Fluorescence assay of the specificity of human plasma and bovine liver phospholipid transfer proteins. *Biochim Biophys Acta* 1985;835:124–31.
- [36] Huuskonen J, Olkkonen VM, Jauhainen M, Metso J, Somerharju P, Ehnholm C. Acyl chain and headgroup specificity of human plasma phospholipid transfer protein. *Biochim Biophys Acta* 1996;1303:207–14.
- [37] Rao R, Albers JJ, Wolfbauer G, Pownall HJ. Molecular and macromolecular specificity of human phospholipid transfer protein. *Biochemistry* 1997;36:3645–53.
- [38] Lagrost L, Athias A, Gambert P, Lallemand C. Comparative study of phospholipid transfer activities mediated by cholesteryl ester transfer protein and phospholipid transfer protein. *J Lipid Res* 1994;35:825–35.
- [39] Lagrost L, Barter PJ. Effects of various non-esterified fatty acids on the transfer of cholesteryl esters from HDL to LDL induced by the cholesteryl ester transfer protein. *Biochim Biophys Acta* 1991;1085:209–16.
- [40] Lagrost L. The role of cholesteryl ester transfer protein and phospholipid transfer protein in the remodeling of plasma high-density lipoproteins. *Trends Cardiovasc Med* 1997;7:27–33.