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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 854 – 860
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Fasting cholesteryl ester transfer protein concentration is independently associated with the postprandial decrease in high-density lipoprotein cholesterol concentration after fat-rich meals: the Hoorn prandial study

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Received 7 July 2009; accepted 2 October 2009

Abstract

The aim of the study was to test whether fasting or postprandial cholesteryl ester transfer protein (CETP) concentrations are associated with postprandial changes in high-density lipoprotein cholesterol (HDL-c) concentrations after fat-rich or carbohydrate-rich meals. Postmenopausal women (76 with normal glucose metabolism [NGM], 41 with type 2 diabetes mellitus [T2DM], and 38 T2DM women with statin therapy [T2DM-ST]) received 2 consecutive fat-rich or carbohydrate-rich meals on separate occasions. Linear regression analysis was performed to assess the associations of fasting CETP and postprandial changes of CETP with postprandial changes in HDL-c. Mean plasma HDL-c concentrations decreased significantly after the fat-rich meals: 0.18 ± 0.09 mmol/L in NGM, 0.16 ± 0.09 mmol/L in T2DM, and 0.14 ± 0.08 mmol/L in T2DM-ST women. This effect was smaller after using carbohydrate-rich meals: 0.12 ± 0.09 mmol/L in the NGM, 0.12 ± 0.08 mmol/L in the T2DM, and 0.10 ± 0.05 mmol/L in the T2DM-ST study group. Higher fasting but not postprandial CETP concentrations were associated with a larger postprandial decrease in HDL-c (β −0.034; 95% confidence interval, −0.067 to −0.001) after the fat-rich meals. This association was independent of the postprandial increase in triglycerides and similar among the 3 study groups. A high fasting CETP concentration may contribute to the postprandial atherogenic lipoprotein profile in postmenopausal women by decreasing HDL-c after fat-rich meals. This effect is independent from the postprandial increase in triglycerides.

1. Introduction

Patients with type 2 diabetes mellitus (T2DM), and in particular postmenopausal women with T2DM, have an increased risk of cardiovascular disease [1], which can in part be ascribed to abnormalities in lipid metabolism [2]. The lipid profile in T2DM is among others characterized by elevated levels of plasma triglycerides in the fasting and in the postprandial state and by low levels of plasma high-density lipoprotein cholesterol (HDL-c) [3]. In addition, it has been demonstrated that the postprandial increase in triglyceride levels after a liquid fat-load is accompanied by a decrease in plasma HDL-c [4-6]. Because low HDL-c is an independent and strong risk factor for future cardiovascular events, this decrease may contribute to the enhanced cardiovascular risk associated with postprandial hypertriglyceridemia [7].

Postprandial triglycerides may influence HDL-c metabolism through the action of cholesteryl ester transfer protein (CETP), which plays a crucial role in lipid homeostasis by mediating the transfer of esterified cholesterol from HDL to apolipoprotein B–containing lipoproteins in exchange for triglycerides [8,9]. Indeed, it is well known that the activity of CETP is highly dependent on the composition and concentration of substrate [10,11]; but it is unknown whether interindividual variation in the level of CETP in plasma affects postprandial lipid metabolism. Nevertheless, elevated levels of CETP have been associated with future coronary

Institutional approval: The study was approved by the ethics committee of the VU University Medical Center and all women gave written informed consent.

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0026-0495/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.10.002

artery disease in the presence of high levels of triglycerides [12]; so diet may play a role in the atherogenicity of CETP.

Until now, most studies that addressed the effect of food consumption on plasma HDL-c levels were small and used a single, nonphysiologic fat load [4-6,13-16]. Instead of applying a single meal, sequential meal intake mimics daily food intake, which is relevant because triglyceride responses to a second meal differ from those after the first meal. Triglycerides are increasing above the levels of the first meal, and sequential meal ingestion provokes a rapid release of triglycerides from the previous meal [17]. Moreover, the possible differences in effects of fat-rich and carbohydrate-rich meals on HDL-c were not investigated. The aim of the present study was to assess the relationship of fasting and postprandial CETP concentration with postprandial changes in HDL-c concentration after 2 consecutive fat-rich or carbohydrate-rich meals. Because most of the T2DM patients use hydroxymethylglutaryl–coenzyme A reductase inhibitors (statins) that are known to affect plasma CETP concentrations, we studied postmenopausal women with T2DM, postmenopausal women with T2DM on statin therapy (T2DM-ST), and postmenopausal women with normal glucose metabolism (NGM).

2. Methods

2.1. Study population

For the Hoorn prandial study, 3 groups of participants were recruited as described earlier [18]. In brief, women with T2DM were recruited from the registry of the Diabetes Care System in the city of Hoorn, the Netherlands. The T2DM patients using statins were considered as a separate study group (denoted as *T2DM-ST*). Women with NGM were randomly selected from the municipal registry of Hoorn. These individuals underwent a 75-g oral glucose tolerance test to verify their glucose tolerance status (fasting glucose <6.1 mmol/L and 2-hour postload glucose <7.8 mmol/L [19]) and were excluded if they used statins.

All women were aged 50 to 65 years. Furthermore, the following exclusion criteria were used: premenopausal status; smoking; untreated endocrine disorders other than T2DM; use of short-acting insulin analogues, thiazolidinediones, fibrates, oral corticosteroids, or hormone replacement therapy; glycosylated hemoglobin (HbA_{1c}) greater than 9.0%; fasting cholesterol greater than 8.0 mmol/L; fasting triglycerides greater than 4.0 mmol/L; and systolic blood pressure greater than 190 mm Hg.

All women gave written informed consent, and the study was approved by the ethics committee of the VU University Medical Center.

2.2. Study design and test meals

After the screening visit, participants attended 2 test-meal visits with a maximum of 1 month apart. On separate occasions and in random order, the participants received 2 consecutive identical fat-rich meals or 2 consecutive carbohydrate-rich meals. Women arrived at the test facility in the morning after an overnight fast. Blood samples were taken before breakfast ($t = 0$) and at $t = 1, 2, 4, 6$, and 8 hours after ingestion of the first meal. The second meal in the form of lunch was given at $t = 4$ hours, immediately after the blood sample was drawn. The nutrient composition of the meals was calculated from the Dutch Nutrient Database [20]. The fat-rich meals consisted of 2 croissants, butter, cheese, and fat-rich milk (3349 kJ; 50 g fat, 56 g carbohydrates, 28 g proteins, and 171 mg cholesterol). The carbohydrate-rich meals consisted of bread, marmalade, cooked chicken breast, ginger bread, and drinkable yogurt enriched with soluble carbohydrates (3261 kJ; 4 g fat, 162 g carbohydrates, 22 g proteins, and 15 mg cholesterol). Participants refrained from other foods, drinks, and physical activity.

2.3. Laboratory analysis

At $t = 0, 1, 2, 4, 6$, and 8 hours, serum HDL-c and triglycerides and fasting cholesterol levels were measured by enzymatic colorimetric assays (Roche, Mannheim, Germany) [21]. Plasma glucose levels were determined with a glucose hexokinase method (Gluco-quant, Roche Diagnostics), and HbA_{1c} was measured with cation-exchange chromatography (Menarini Diagnostics, Florence, Italy). Insulin was measured in serum with an immunometric assay in which proinsulin did not cross-react (Advia Centaur; Bayer Diagnostics, Mijdrecht, the Netherlands). The CETP concentration was measured at $t = 0, 2, 4$, and 8 hours with a 2-antibody sandwich immunoassay, which was developed and described by Niemeijer-Kanters et al [22]. Interassay and intraassay coefficients of variation were 7.8% and 6.0%, respectively. As a standard, pool plasma from healthy volunteers containing 2 mg/L CETP was used.

2.4. Statistical analyses

Analyses were performed in SPSS 14.0.1 for Windows (SPSS, Chicago, IL). Differences in characteristics between the 3 study groups were tested with analysis of variance with post hoc comparisons. In case of skewed distribution, variables were ln-transformed before analyses. Postprandial concentrations were tested with paired-samples t test for comparison with the concentration at $t = 0$.

Linear regression analysis was performed with the postprandial change in HDL-c (ΔHDL-c = HDL-c_{t8} − HDL-c_{t0}) as an outcome variable. In the first model, we included fasting CETP concentration as independent variable. We investigated whether the association between CETP concentration and ΔHDL-c was different for NGM, T2DM, or T2DM-ST women by adding product terms (T2DM∗CETP concentration and T2DM-ST∗CETP concentration) as a covariate to the first model. Because of $P > .10$ for these product terms, the 3 study groups were combined;

Table 1
Characteristics of the study population

	NGM	T2DM	T2DM-ST
n	76	41	38
Age (y)	60.1 (4.0)	58.9 (3.7)	61.2 (4.1)*
BMI (kg/m^2)	26.3 (3.6)	32.7 (6.0)†	30.6 (4.6)†
Fasting glucose (mmol/L)[a]	5.2 (0.4)	7.1 (1.4)†	7.5 (1.2)†
HbA_{1c} (%)	5.6 (0.3)	6.6 (0.6)†	6.8 (0.7)†
Fasting insulin (pmol/L)[a]	33.2 (25.5-47.5)	82.5 (39.3-127.0)†	87.1 (54.9-130.7)†
Use of insulin (%)	–	17	21
Total cholesterol (mmol/L)[a]	5.7 (0.8)	5.5 (1.0)	4.4 (0.8)*,†
LDL cholesterol (mmol/L)[a]	3.5 (0.8)	3.4 (0.9)	2.2 (0.7)*,†

Means (SD). Median (interquartile range) in case of skewed distribution. BMI indicates body mass index.

[a] Based on the mean of 2 fasting measurements derived from the 2 test-meal visits.

* $P < .05$ compared with T2DM group.

† $P < .05$ compared with NGM group.

and all models were adjusted for age, T2DM, and use of statin medication. In a second model, we adjusted for the effect of fasting HDL-c and triglycerides on ΔHDL-c. To further adjust for the known effect of postprandial triglyceride levels (Δtriglycerides = $\text{triglycerides}_{t8}$ − $\text{triglycerides}_{t0}$) on ΔHDL-c, we added this in a third model. In a fourth model, we evaluated whether postprandial changes in CETP concentration (ΔCETP = CETP_{t8} − CETP_{t0}) were associated with postprandial HDL-c changes.

Except for interaction terms where we used a P value < .10, we considered a 2-sided P value < .05 to indicate statistical significance.

3. Results

3.1. Characteristics

Characteristics of the study population are given in Table 1. Women in the T2DM-ST group were slightly older as compared with women with T2DM who did not use statin medication. Furthermore, women with diabetes had higher body mass index, fasting glucose, HbA_{1c}, and insulin levels as compared with women with NGM. Plasma cholesterol and low-density lipoprotein cholesterol concentrations were lower in the T2DM-ST group as compared with the NGM and T2DM groups.

3.2. Postprandial responses

Fasting plasma triglycerides were significantly higher and plasma HDL-c concentrations were lower in women with T2DM as compared with women with NGM (Table 2). The effects of 2 consecutive fat-rich meals and carbohydrate-rich meals on triglyceride, HDL-c, and CETP concentration are shown in Table 2 and Fig. 1. The use of 2 consecutive fat-rich meals resulted in a steep increase of plasma triglyceride levels ($P < .01$, Table 2), which was similar among the 3 study groups. Concomitantly, plasma HDL-c levels decreased after the fat-rich meals in all study groups ($P < .01$). The consumption of 2 carbohydrate-rich meals resulted in a less pronounced increase in plasma triglycerides ($P < .01$) and decrease in plasma HDL-c ($P < .01$). These effects were again similar among the 3 study groups (Table 2).

Fasting plasma CETP concentrations were nearly identical in women with T2DM and NGM, but lower in the T2DM-ST group ($P < .05$, Table 2). However, in all groups, a similar increase in CETP was observed after the fat-rich and the carbohydrate–rich meals, which just reached statistical significance after the fat-rich meals in the T2DM

Table 2
Fasting levels and postprandial changes ($t8 - t0$) of plasma HDL-c, triglycerides, and CETP after 2 consecutive fat-rich or carbohydrate-rich meals

	NGM	T2DM	T2DM-ST
Fat-rich meals			
Fasting HDL-c (mmol/L)	1.61 (0.43)	1.35 (0.31)*	1.31 (0.28)*
ΔHDL-c (mmol/L)	−0.18 (0.09)†	−0.16 (0.09)†	−0.14 (0.08)*,†
Fasting triglycerides (mmol/L)	1.0 (0.8 to 1.4)	1.8 (1.2 to 2.3)*	1.7 (1.3 to 2.3)*
ΔTriglycerides (mmol/L)	1.0 (0.6)†	1.2 (0.9)†	1.2 (0.9)†
Fasting CETP (mg/L)	1.76 (0.41)	1.78 (0.34)	1.54 (0.41)*,‡
ΔCETP (mg/L)	0.06 (0.31)	0.09 (0.29)†	0.07 (0.21)
Carbohydrate-rich meals			
Fasting HDL-c (mmol/L)	1.64 (0.44)	1.37 (0.28)*	1.34 (0.31)*
ΔHDL-c (mmol/L)	−0.12 (0.09)†	−0.12 (0.08)†	−0.10 (0.05)†
Fasting triglycerides (mmol/L)	1.0 (0.9 to 1.4)	1.5 (1.2 to 2.1)*	1.6 (1.2 to 2.3)*
ΔTriglycerides (mmol/L)	0.3 (0.3)†	0.4 (0.4)†	0.3 (0.3)†
Fasting CETP (mg/L)	1.78 (0.36)	1.82 (0.53)	1.58 (0.36)*,‡
ΔCETP (mg/L)	0.07 (0.23)†	0.00 (0.34)	0.03 (0.24)

Means (SD). Median (interquartile range) in case of skewed distribution.

* $P < .05$ compared with NGM group.

† Significant postprandial change on $t8$ as compared with $t0$ ($P < .05$).

‡ $P < .05$ compared with T2DM group.

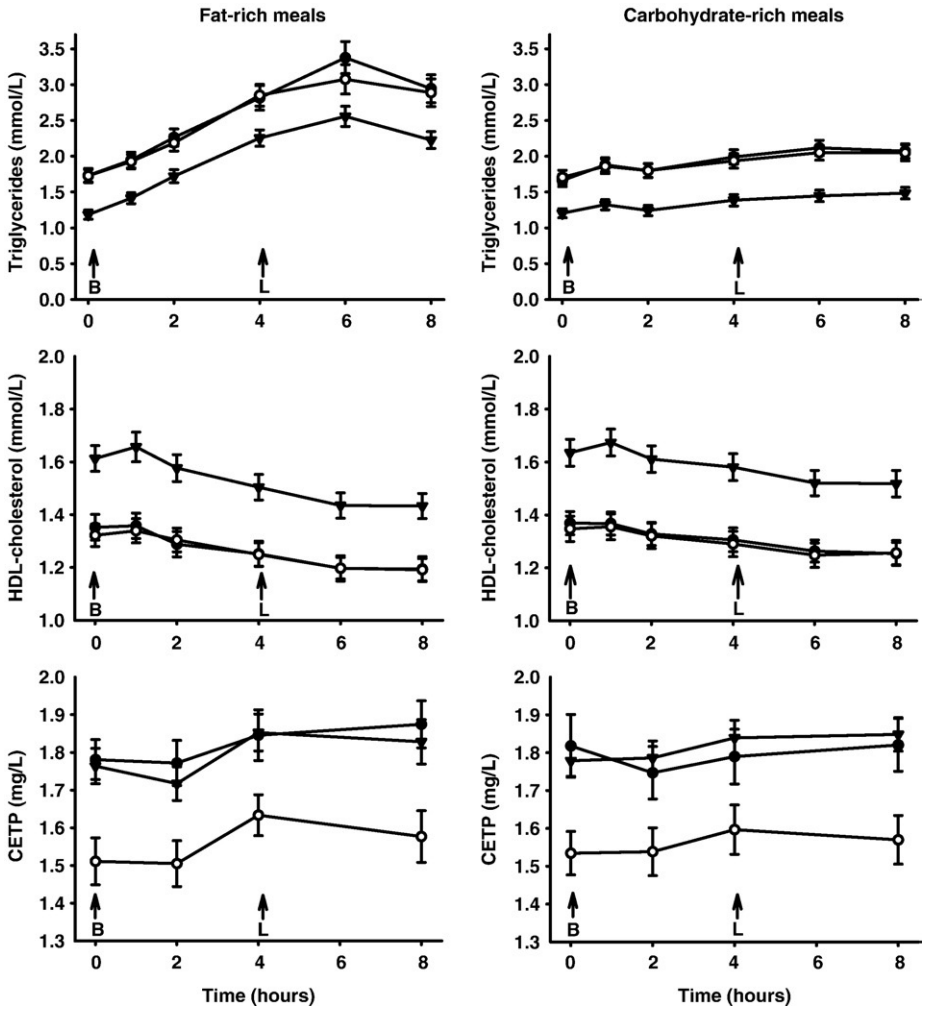

Fig. 1. Triglycerides, HDL-c, and CETP concentrations (means ± SEM) after ingestion of 2 consecutive meals. NGM (▼), T2DM (●), and T2DM-ST (○). B indicates breakfast; L, lunch.

group ($P < .05$, Table 2) and after the carbohydrate-rich meals in the NGM study group ($P < .05$, Table 2). Analyses in the combined group revealed a significant increase in CETP concentration after the fat-rich (ΔCETP = 0.07 mg/L, $P < .01$) but not after the carbohydrate-rich meals (ΔCETP = 0.04 mg/L, not significant).

3.3. CETP concentration and postprandial HDL-c

In further analyses, we investigated whether plasma CETP concentrations were responsible for the postprandial decrease in plasma HDL-c levels and whether this relationship depends on the postprandial increase in triglycerides. Because the relation between CETP concentration and ΔHDL-c after fat-rich and carbohydrate-rich meals was similar in the NGM, T2DM, and T2DM-ST subgroups (P values for interaction > .10), these study groups were combined for further analyses (Table 3).

When adjusted for age, diabetic state, and use of statin medication only, fasting CETP concentration was not significantly associated with ΔHDL-c after the fat-rich or the carbohydrate-rich meals (Table 3, model 1).

In model 2, fasting HDL-c and triglyceride levels were added to the model. These variables were inversely and significantly associated with ΔHDL-c after the fat-rich meals, but the association between fasting CETP concentration and ΔHDL-c was slightly attenuated as compared with model 1. In model 3, we added Δtriglycerides, which was inversely and significantly associated with ΔHDL-c. In contrast to model 2, fasting triglyceride levels did not significantly contribute to this model, whereas fasting CETP concentrations were significantly associated with ΔHDL-c after the fat-rich meals. Adding ΔCETP (model 4) did not alter the associations of fasting CETP concentration and Δtriglycerides with ΔHDL-c.

Calculating the change in triglycerides as the difference between $t6$ and $t0$ and the change in CETP concentration as the difference between $t4$ and $t0$, which is the peak in both postprandial responses, the data as presented in model 3 and 4 did not essentially change (data not shown).

Table 3
Linear regression analysis with postprandial change in HDL-c concentrations ($t8 - t0$) after 2 consecutive fat-rich or carbohydrate-rich meals

	ΔHDL-c (fat-rich meals)[a]	ΔHDL-c (carbohydrate-rich meals)[b]
Crude model		
Fasting CETP (mg/L)	−0.042 (−0.077 to −0.007)*	−0.021 (−0.050 to 0.009)
Model 1		
Fasting CETP (mg/L)	−0.032 (−0.069 to 0.004)	−0.015 (−0.045 to 0.016)
Model 2		
Fasting CETP (mg/L)	−0.029 (−0.064 to 0.006)	−0.021 (−0.051 to 0.009)
Fasting HDL-c (mmol/L)	−0.092 (−0.133 to −0.051)*	−0.040 (−0.078 to −0.002)*
Ln fasting triglycerides (mmol/L)	−0.063 (−0.102 to −0.024)*	0.018 (−0.019 to 0.051)
Model 3		
Fasting CETP (mg/L)	−0.034 (−0.067 to −0.001)*	−0.013 (−0.044 to 0.018)
Fasting HDL-c (mmol/L)	−0.101 (−0.139 to −0.063)*	−0.043 (−0.081 to −0.005)*
Ln fasting triglycerides (mmol/L)	−0.029 (−0.069 to 0.010)	0.019 (−0.018 to 0.056)
ΔTriglycerides (mmol/L)[c]	−0.042 (−0.060 to −0.024)*	−0.032 (−0.067 to 0.003)
Model 4		
Fasting CETP (mg/L)	−0.035 (−0.068 to −0.002)*	−0.007 (−0.040 to 0.027)
Fasting HDL-c (mmol/L)	−0.102 (−0.140 to −0.063)*	−0.042 (−0.079 to −0.004)*
Ln fasting triglycerides (mmol/L)	−0.031 (−0.071 to 0.009)	0.016 (−0.021 to 0.054)
ΔTriglycerides (mmol/L)[c]	−0.041 (−0.059 to −0.022)*	−0.034 (−0.069 to 0.001)
ΔCETP (mg/L)[c]	−0.018 (−0.063 to 0.027)	0.026 (−0.024 to 0.075)

Models 1 to 4 were adjusted for age, diabetic state, and use of statin medication.

[a] Independent variables in this model were derived from the fat-rich meals.

[b] Independent variables in this model were derived from the carbohydrate-rich meals.

[c] Δ was calculated as concentration on $t = 8$ minus concentration on $t = 0$.

* $P < .05$.

4. Discussion

This study among individuals with and without diabetes demonstrates a postprandial decrease in HDL-c concentrations after 2 consecutive fat-rich meals. A similar but less pronounced decrease in HDL-c was seen after 2 carbohydrate-rich meals. The change in HDL-c concentration after fat-rich meals was inversely and independently related to fasting CETP concentrations, fasting HDL-c, and postprandial changes in triglycerides. These associations were not affected by the diabetic state or use of statin medication. The postprandial changes in CETP concentration were not related to the postprandial change in HDL-c levels.

4.1. HDL-c decrease in the postprandial phase

The postprandial decrease of HDL-c after fat-rich meals is in line with previous studies. Earlier studies were performed in obese [4], smoking [5], hypertriglyceridemic [14], or healthy persons [16] and in patients with T2DM [13], coronary artery disease [15], or metabolic syndrome [6]. Most of them showed a decrease in HDL-c; but some did not, which might be due to a smaller sample size, the use of a single instead of a sequential fat-load, and the variation in study period after meal intake. Our data demonstrate for the first time that physiologic meals induce a significant decrease of HDL-c in healthy women as well as those with T2DM. We also compared the effect of fat-rich meals vs carbohydrate-rich meals and found that both decrease HDL-c concentrations significantly, although the carbohydrate-rich meals clearly showed a less pronounced effect. As suggested earlier, the decrease of HDL-c is possibly the result of an increased cholesterol ester transfer that is stimulated by the postprandial availability of triglycerides. This is in line with the present finding that the decrease in HDL-c is smaller after the carbohydrate-rich meal. The present study shows that this phenomenon is also associated with fasting CETP concentration. Apparently, the level of CETP in the circulation does, at least in part, influence the amount of cholesterol esters that is transferred from HDL to apolipoprotein B–containing lipoproteins, resulting in the presently observed decrease in HDL-c. Because there exists a strong correlation between CETP concentration and CETP activity (as measured with exogenous substrates [23]), it is likely that an increase in CETP concentration in the circulation is reflected by increased CETP activity. Some studies indeed support this notion by reporting a postprandial increase in CETP concentration in addition to an increase in CETP activity [24], whereas other studies did not [13,25]. In plasma, the extent of cholesterol ester transfer is highly dependent upon the concentration and composition of the endogenous substrate [10,11], as reflected by the inverse relation between postprandial triglycerides and postprandial HDL-c in the present study.

Since the failure of the CETP inhibitor torcetrapib to reduce cardiovascular events, the therapeutic inhibition of CETP has been subject of debate [26]. Despite this, a recent meta-analysis of genetic studies showed that genetic variants associated with reduced CETP activity and elevated HDL-c levels are also associated with a modest protection against cardiovascular disease [27]. Data on the relationship between CETP plasma levels and cardiovascular risk are less

consistent. It has been suggested that the metabolic setting, especially the level of triglycerides, determines whether CETP is associated with an increased risk for coronary artery disease [12,28]. The present results suggest that diet may affect the complex relation of CETP with atherosclerosis.

4.2. Effect of statin treatment on postprandial lipid metabolism

The decrease in HDL-c after the fat-rich meal was similar in the T2DM and T2DM-ST study groups. This is in agreement with a study in patients with the metabolic syndrome showing a decrease in HDL-c levels that was independent of lipid-lowering therapy [6]. Furthermore, statins reduce plasma CETP concentration by acting on CETP gene expression in the liver due to inhibition of cholesterol synthesis [29]. Indeed, in the present study, the patients with T2DM who were treated with statins had a lower fasting CETP concentration. However, we have demonstrated that, despite lower baseline levels, the postprandial HDL-c and CETP responses were not different during statin treatment.

4.3. CETP concentration in the postprandial state

The postprandial increase in CETP concentration is in line with 2 previous studies in normolipidemic subjects after an oral liquid fat load [24] and after a fat-rich meal in hypercholesterolemic women [25]. The lack of significant postprandial increase in CETP concentration in other studies may be due to the limited number of subjects [13]. The current study (largest in its kind) also showed similar postprandial increases in plasma CETP concentration among healthy individuals and patients with T2DM with or without statin medication, suggesting that plasma lipid and glucose concentrations do not affect this phenomenon.

The rise of CETP may be the result of increased cellular secretion of CETP by liver and/or adipose tissue stores because CETP is known to be regulated by posttranslational mechanisms [30]. However, Radeau et al [31] demonstrated a close correlation between adipose tissue CETP messenger RNA abundance and plasma CETP concentrations (r = 0.85), which appears to argue against intracellular storage of CETP. Further in vivo studies are required to elucidate the possible role of posttranslational regulation of CETP in liver or adipose tissue.

4.4. Strengths and limitations of the study

Strengths of the present study are the relatively large number of persons studied and a direct comparison of the effects of 2 physiologic fat-rich and carbohydrate-rich meals. A limitation is that only postmenopausal women were investigated. Caution should therefore be exercised in extrapolating the present data to effects in premenopausal women and men, especially because it has been reported that CETP gene expression is influenced by sex hormones [30].

Another potential limitation is that we have no data on cholesterol ester transfer. However, cholesterol ester transfer is expected to be strongly related to the postprandial decrease in HDL-c because the rate of exchange is known to be highly dependent on the availability of substrate [10]. Indeed, we observed a strong inverse relationship between postprandial triglyceride levels and postprandial HDL-c.

4.5. Conclusions and implications

To conclude, in a large group of postmenopausal women with and without T2DM, fat-rich and, to a lesser extent, carbohydrate-rich meals induce a significant decrease of plasma HDL-c concentration. Fasting CETP levels and postprandial changes in triglyceride levels are both inversely and independently related to these changes in HDL-c observed after fat-rich meals. Fasting plasma CETP concentration may contribute to the postprandial atherogenic lipoprotein profile in postmenopausal women by decreasing HDL-c levels.

Acknowledgment

The Hoorn prandial study was financially supported by a grant from the Dutch Diabetes Research Foundation (grant 2001.00.052) and by funding from Novartis International, Switzerland. The authors thank Alinda Schimmel for performing the CETP measurements.

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