The puzzle of high-density lipoprotein in cardiovascular prevention

El-Harchaoui, Abdelkarim

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Fasting plasma CETP concentration is independently associated with the postprandial decrease in HDL cholesterol concentration following fat-rich meals: The Hoorn prandial study

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ABSTRACT

**Background:** The postprandial increase in triglycerides following a fat-load is accompanied by a decrease in plasma high-density lipoprotein (HDL) cholesterol.

**Aim:** To test whether fasting or postprandial CETP concentrations are associated with postprandial changes in HDL cholesterol concentrations following fat-rich or carbohydrate-rich meals in women with and without type 2 diabetes (T2DM).

**Methods:** The study population consisted of 76 women with normal glucose metabolism (NGM), 41 with T2DM and 38 T2DM women with statin therapy (T2DM-ST). They received two 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 (CETP<sub>t8</sub>-CETP<sub>t0</sub>) with postprandial changes in HDL cholesterol (HDL cholesterol<sub>t8</sub>-HDL cholesterol<sub>t0</sub>).

**Results:** Mean plasma HDL cholesterol concentrations decreased significantly in all groups 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. The decrease in HDL cholesterol levels following the carbohydrate-rich meals was smaller; 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 CETP concentrations were associated with a larger postprandial decrease in HDL cholesterol (Beta -0.034 [95% CI -0.067;-0.001]) following the fat-rich meals, independent of the postprandial increase in triglycerides and similar among the three study groups. The postprandial increase in CETP concentration was not associated with postprandial changes in HDL cholesterol.

**Conclusion:** A high plasma CETP concentration may contribute to the postprandial atherogenic lipoprotein profile in postmenopausal women by decreasing HDL cholesterol after fat-rich meals. This effect is independent from the postprandial increase in triglycerides.
INTRODUCTION

Patients with type 2 diabetes (T2DM), and in particular postmenopausal women, 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 characterized by elevated levels of plasma triglycerides in the fasting and in the postprandial state and by low levels of plasma high-density lipoprotein (HDL) cholesterol (3). It has recently been shown that non-fasting triglyceride levels predict cardiovascular risk better than fasting plasma triglycerides, emphasizing the importance of the postprandial state (4,5). Also, it has been demonstrated that the postprandial increase in triglyceride levels following a liquid fat-load is accompanied by a decrease in plasma HDL cholesterol (6-8). Since low HDL cholesterol is an independent and strong risk factor for future cardiovascular events, this decrease may contribute to the enhanced cardiovascular risk associated with postprandial hypertriglyceridemia (9).

Postprandial triglycerides may influence HDL cholesterol 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 (10,11). However, it is unknown whether plasma CETP concentrations affect postprandial changes in HDL cholesterol and whether this effect depends on the level of hypertriglyceridemia.

Until now, a limited number of studies have investigated the effect of food consumption on plasma HDL cholesterol levels. Most studies were small and used a single, non-physiological liquid fat-load (6-8,12-15). Moreover, the possible differences in effects of fat-rich and carbohydrate-rich meals on HDL cholesterol as well as the effect of two consecutive physiological meals have not been investigated to date. The aim of the present study was to assess the relationship of fasting and postprandial CETP concentration with the magnitude of postprandial changes in HDL cholesterol concentration following two consecutive fat-rich or carbohydrate-rich meals. Since most of the T2DM patients use HMG-CoA reductase inhibitors (statins) which 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).

METHODS

Study population

For the Hoorn prandial study, three groups of participants were recruited as described earlier (16). 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 who had uncontrolled T2DM (glycosylated
hemoglobin [HbA1c] >9.0%) were excluded. 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 post-load glucose <7.8 mmol/l (17)) and were excluded if they used statins.

All women were aged 50-65 years and for all women, the following exclusion criteria were employed: pre-menopausal status (menses in the last 12 months), smoking, untreated endocrine disorders other than T2DM, use of short-acting insulin analogues, use of thiazolidinediones and fibrates, use of oral corticosteroids, use of hormone replacement therapy, fasting cholesterol >8.0 mmol/l, fasting triglycerides >4.0 mmol/l, systolic blood pressure >190 mmHg, liver or renal impairment.

Weight and height were measured twice in barefooted participants wearing light clothes only. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m). All women gave written informed consent and the study was approved by the ethics committee of the VU University Medical Center.

Study design and test meals
Following the screening visit, participants attended two test-meal visits with a maximum of one month apart. On separate occasions and in random order, the participants received two consecutive identical fat-rich meals or two 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=4h, immediately after the blood sample was drawn. The nutrient composition of the meals was calculated from the Dutch Nutrient Database (18). 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). Meals were eaten within a 10 minutes timeframe. Except for water (available ad libitum), participants refrained from other foods and drinks. Throughout a visit day, physical activity was limited to a short walk between two adjacent rooms.

Laboratory analysis
At t=0, 1, 2, 4, 6 and 8h time points serum HDL cholesterol and triglycerides and fasting cholesterol levels were measured by enzymatic colorimetric assays (Roche, Mannheim, Germany) (19). Plasma glucose levels were determined with a glucose hexokinase method (Gluco-quant, Roche Diagnostics, Mannheim, Germany) and HbA1c was measured with cation-exchange chromatography (Menarini Diagnostics, Florence, Italy). Insulin was measured in serum by an immunometric assay in which proinsulin did not cross-react (Advia Centaur, Bayer Diagnostics, Mijdrecht, The Netherlands). CETP concentration was measured at t=0, 2, 4, and 8h by a
two-antibody sandwich immunoassay, which was developed and described by Niemeijer-Kant-ers et al (20). Inter-assay and intra-assay 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.

**Statistical analyses**

Analyses were performed in SPSS 14.0.1 for Windows (SPSS Inc. Chicago, IL). Differences in characteristics between the three study groups were tested with ANOVA 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 cholesterol ($\Delta$HDL-C = HDL-C$_{t8}$ - HDL-C$_{t0}$) following fat-rich and carbohydrate-rich meals 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 $\Delta$HDL cholesterol 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 these interaction terms were non-significant ($P$>0.10), the three study groups were combined and all models were adjusted for age, T2DM and use of statin medication. In a second model, we investigated whether the association between CETP concentration and $\Delta$HDL cholesterol was independent of fasting HDL cholesterol and triglycerides and therefore, we adjusted for these variables. To further adjust for the known effect of postprandial triglyceride levels on $\Delta$HDL cholesterol, we added the postprandial change in triglycerides ($\Delta$triglycerides = triglycerides$_{t8}$ - triglycerides$_{t0}$) in a third model. In a fourth model, we evaluated whether postprandial changes in CETP concentration ($\Delta$CETP = CETP$_{t8}$ - CETP$_{t0}$) determined postprandial HDL cholesterol changes.

Except for interaction terms where we used a $P$-value<0.10, we considered a two-sided $P$-value <0.05 to indicate statistical significance.

**RESULTS**

**Characteristics**

Characteristics of the study population are described in Table 1. Irrespective of use of statins, T2DM women were more obese, had higher fasting plasma glucose, higher HbA1c and higher insulin levels than women with NGM. In the T2DM-ST group, plasma cholesterol and LDL cholesterol concentrations were lower as compared to the NGM and T2DM groups. Of all the women with T2DM (n=79), 65% used anti-hypertensive medication and 73% used oral blood glucose lowering medication.
postprandial responses

Fasting plasma triglycerides were higher and plasma HDL cholesterol concentrations were lower in women with T2DM as compared to women with NGM (Table 2). The effects of two consecutive fat-rich meals and two consecutive carbohydrate-rich meals on triglyceride, HDL cholesterol and CETP concentration in each of the three study groups are shown in Table 2 and Figure 1. The use of two consecutive fat-rich meals resulted in a steep increase of plasma triglyceride levels (\( P < 0.01 \)), which was similar among the three study groups. Concomitantly, plasma HDL cholesterol levels decreased following the fat-rich meals in all study groups (\( P < 0.01 \)). The consumption of two carbohydrate-rich meals resulted in a less pronounced increase in plasma triglycerides (\( P < 0.01 \)) and decrease in plasma HDL cholesterol (\( P < 0.01 \)), both responses being similar among the three study groups (Table 2).

Fasting plasma CETP concentrations were nearly identical in women with T2DM and NGM. In the T2DM-ST group, however, plasma CETP concentrations were significantly lower compared to the other two groups (\( P < 0.05 \), Table 2). A significant increase in CETP concentration following the fat-rich meals was found in the T2DM group (\( P < 0.05 \), Table 2) and a significant increase was found following the carbohydrate-rich meals in the NGM study group (\( P < 0.05 \), Table 2). Because the increase in CETP concentration did not significantly differ between the study groups, we additionally analyzed the increase in CETP concentration in the combined study population. A significant increase in CETP concentration following the fat-rich (\( \Delta \text{CETP}=0.07 \text{mg/l, } P<0.01 \)) but not following the carbohydrate rich meals (\( \Delta \text{CETP}=0.04 \text{mg/l, N.S.} \)) was observed.

CETP concentration and postprandial HDL cholesterol

Associations between fasting CETP concentration and \( 
\Delta \text{HDL cholesterol} \) following the fat-rich and the carbohydrate-rich meals are shown in Table 3. The relation between CETP concentration

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### Table 1. Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>NGM</th>
<th>T2DM</th>
<th>T2DM-ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>76</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.1 (4.0)</td>
<td>58.9 (3.7)</td>
<td>61.2 (4.1) b</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (3.6)</td>
<td>32.7 (6.0) c</td>
<td>30.6 (4.6) c</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L) a</td>
<td>5.2 (0.4)</td>
<td>7.1 (1.4) c</td>
<td>7.5 (1.2) c</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 (0.3)</td>
<td>6.6 (0.6) c</td>
<td>6.8 (0.7) c</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L) a</td>
<td>33.2 (25.5 to 47.5)</td>
<td>82.5 (39.3 to 127.0) c</td>
<td>87.1 (54.9 to 130.7) c</td>
</tr>
<tr>
<td>Use of insulin (%)</td>
<td>-</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L) a</td>
<td>5.7 (0.8)</td>
<td>5.5 (1.0)</td>
<td>4.4 (0.8) b,c</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L) a</td>
<td>3.5 (0.8)</td>
<td>3.4 (0.9)</td>
<td>2.2 (0.7) b,c</td>
</tr>
</tbody>
</table>


a Based on the mean of two fasting measurements derived from the two test-meal visits.
b \( P < 0.05 \) compared to T2DM group.
c \( P < 0.05 \) compared to NGM group.
and ΔHDL cholesterol was similar in the NGM, T2DM and T2DM-ST subgroups (P-values for interaction >0.10). Therefore, the three study groups were combined for further analyses.

When adjusted for age, diabetic state and use of statin medication only, fasting CETP concentration was not significantly associated with ΔHDL cholesterol following the fat-rich or the carbohydrate-rich meals (Table 3, model 1). The proportion of variance (R²) explained by model 1 was 0.07 and 0.03 for ΔHDL cholesterol following fat-rich meals and carbohydrate-rich meals respectively.

In model 2, fasting HDL cholesterol and triglyceride levels were inversely and significantly associated with ΔHDL cholesterol following the fat-rich meals and carbohydrate-rich meals (Table 3, model 2). The proportion of variance (R²) explained by model 2 was 0.29 and 0.11 for ΔHDL cholesterol following fat-rich meals and carbohydrate-rich meals respectively. Adding ΔΔCETP (model 4) did not alter the associations of fasting CETP concentration and ΔΔtriglycerides with ΔHDL cholesterol.

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 2. Fasting levels and postprandial changes (t8-t0) of plasma HDL cholesterol, triglycerides and CETP, following two consecutive fat-rich or carbohydrate-rich meals

<table>
<thead>
<tr>
<th></th>
<th>NGM</th>
<th>T2DM</th>
<th>T2DM-ST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat-rich meals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting HDL-cholesterol (mmol/L)</td>
<td>1.61 (0.43)</td>
<td>1.35 (0.31)</td>
<td>1.31 (0.28)</td>
</tr>
<tr>
<td>ΔHDL-cholesterol (mmol/L)</td>
<td>-0.18 (0.09)</td>
<td>-0.16 (0.09)</td>
<td>-0.14 (0.08)</td>
</tr>
<tr>
<td>Fasting triglycerides (mmol/L)</td>
<td>1.0 (0.8 to 1.4)</td>
<td>1.8 (1.2 to 2.3)</td>
<td>1.7 (1.3 to 2.3)</td>
</tr>
<tr>
<td>Δtriglycerides (mmol/L)</td>
<td>1.0 (0.6)</td>
<td>1.2 (0.9)</td>
<td>1.2 (0.9)</td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>1.76 (0.41)</td>
<td>1.78 (0.34)</td>
<td>1.54 (0.41)</td>
</tr>
<tr>
<td>ΔCETP (mg/L)</td>
<td>0.06 (0.31)</td>
<td>0.09 (0.29)</td>
<td>0.07 (0.21)</td>
</tr>
<tr>
<td><strong>Carbohydrate-rich meals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting HDL-cholesterol (mmol/L)</td>
<td>1.64 (0.44)</td>
<td>1.37 (0.28)</td>
<td>1.34 (0.31)</td>
</tr>
<tr>
<td>ΔHDL-cholesterol (mmol/L)</td>
<td>-0.12 (0.09)</td>
<td>-0.12 (0.08)</td>
<td>-0.10 (0.05)</td>
</tr>
<tr>
<td>Fasting triglycerides (mmol/L)</td>
<td>1.0 (0.9 to 1.4)</td>
<td>1.5 (1.2 to 2.1)</td>
<td>1.6 (1.2 to 2.3)</td>
</tr>
<tr>
<td>Δtriglycerides (mmol/L)</td>
<td>0.3 (0.3)</td>
<td>0.4 (0.4)</td>
<td>0.3 (0.3)</td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>1.78 (0.36)</td>
<td>1.82 (0.53)</td>
<td>1.58 (0.36)</td>
</tr>
<tr>
<td>ΔCETP (mg/L)</td>
<td>0.07 (0.23)</td>
<td>0.00 (0.34)</td>
<td>0.03 (0.24)</td>
</tr>
</tbody>
</table>

Means (SD). Median (interquartile range) in case of skewed distribution. NGM: Normal glucose metabolism, T2DM: type 2 diabetes mellitus, T2DM-ST: type 2 diabetes mellitus using statin medication, CETP: Cholesteryl Ester Transfer Protein

a P<0.05 compared to NGM group.
b Significant postprandial change on t8 as compared to t0 (P<0.05).
c P<0.05 compared to T2DM group.
A pronounced decrease in HDL cholesterol was seen following two carbohydrate-rich meals. 

This study in persons with and without diabetes, demonstrates a postprandial decrease in HDL cholesterol concentrations following two consecutive fat-rich meals. A similar but less pronounced decrease in HDL cholesterol was seen following two carbohydrate-rich meals.

DISCUSSION

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

**Table 3.** Linear regression analysis with postprandial change in HDL cholesterol concentrations (t8-t0) following two consecutive fat-rich or carbohydrate-rich meals

<table>
<thead>
<tr>
<th></th>
<th>ΔHDL cholesterol (fat-rich meals)</th>
<th>ΔHDL cholesterol (carbohydrate-rich meals)</th>
</tr>
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<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>-0.032 (-0.069 to 0.004)</td>
<td>-0.015 (-0.045 to 0.016)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>-0.029 (-0.064 to 0.006)</td>
<td>-0.021 (-0.051 to 0.009)</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mmol/L)</td>
<td>-0.092 (-0.133 to -0.051)</td>
<td>-0.040 (-0.078 to -0.002)</td>
</tr>
<tr>
<td>Ln fasting triglycerides (mmol/L)</td>
<td>-0.063 (-0.102 to -0.024)</td>
<td>0.018 (-0.019 to 0.051)</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>-0.034 (-0.067 to -0.001)</td>
<td>-0.013 (-0.044 to 0.018)</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mmol/L)</td>
<td>-0.101 (-0.139 to -0.063)</td>
<td>-0.043 (-0.081 to -0.005)</td>
</tr>
<tr>
<td>Ln fasting triglycerides (mmol/L)</td>
<td>-0.029 (-0.069 to 0.010)</td>
<td>0.019 (-0.018 to 0.056)</td>
</tr>
<tr>
<td>ΔTriglycerides (mmol/L)</td>
<td>-0.042 (-0.060 to -0.024)</td>
<td>-0.032 (-0.067 to 0.003)</td>
</tr>
<tr>
<td><strong>Model 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting CETP (mg/L)</td>
<td>-0.035 (-0.068 to -0.002)</td>
<td>-0.007 (-0.040 to 0.027)</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mmol/L)</td>
<td>-0.102 (-0.140 to -0.063)</td>
<td>-0.042 (-0.079 to -0.004)</td>
</tr>
<tr>
<td>Ln fasting triglycerides (mmol/L)</td>
<td>-0.031 (-0.071 to 0.009)</td>
<td>0.016 (-0.021 to 0.054)</td>
</tr>
<tr>
<td>ΔTriglycerides (mmol/L)</td>
<td>-0.041 (-0.059 to -0.022)</td>
<td>-0.034 (-0.069 to 0.001)</td>
</tr>
<tr>
<td>ΔCETP (mg/L)</td>
<td>-0.018 (-0.063 to 0.027)</td>
<td>0.026 (-0.024 to 0.075)</td>
</tr>
</tbody>
</table>

All models were adjusted for age, diabetic state and use of statin medication. CETP: cholesteryl ester transfer protein. a Independent variables used in this model were derived from the fat-rich meals. b Independent variables used in this model were derived from the carbohydrate-rich meals. c P<0.05. d Δ was calculated as concentration on t=8 minus concentration on t=0.

The change in HDL cholesterol concentration following fat-rich meals was inversely and independently related to fasting CETP concentrations, fasting HDL cholesterol and postprandial changes in triglycerides. The associations with the postprandial decrease in HDL cholesterol were not affected by the diabetic state or use of statin medication. Furthermore, plasma CETP concentrations increased slightly following fat-rich meals, but not following carbohydrate-rich meals. These postprandial changes in CETP concentration were not related to the postprandial change in HDL cholesterol levels.

**HDL cholesterol decrease in the postprandial phase**

The postprandial decrease of HDL cholesterol following fat-rich meals is in line with previous studies in obese (6), smoking (7), hypertriglyceridemic (13), or in healthy persons (15) and in patients with T2DM (12), coronary artery disease (14) or metabolic syndrome (8). Our data clearly demonstrate that the postprandial decrease in HDL cholesterol occurs both in healthy women and in those with T2DM. Earlier studies were smaller and used a non-physiological high load of triglycerides. We were able to compare the effect of fat-rich meals, containing a physiological amount of fat, with the effect of carbohydrate-rich meals. The use of two consecutive meals more closely reflects reality since most people in the western world eat at regular intervals and are in a postprandial state during most of the day.
It has not been demonstrated before that both fat-rich and carbohydrate-rich meals induce a decrease of HDL cholesterol concentrations, although the carbohydrate rich meals clearly showed a less pronounced effect. As earlier suggested, the decrease of HDL cholesterol is possibly the result of an increased cholesterol ester transfer which is stimulated by the postprandial availability of triglycerides especially following fat-rich meals. The main novelty of the present study is that the postprandial decrease in HDL cholesterol was not only associated with the postprandial increase in triglycerides, but also 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. Of note, a strong correlation exists between CETP concentration and CETP activity as measured with exogenous substrates (21) but not with endogenous substrate. Thus it is likely that an increase in CETP concentration in the circulation is reflected by increased CETP activity as measured with exogenous substrate. Some studies indeed support this notion by reporting a postprandial increase in CETP concentration in addition to an increase in CETP activity (22), whereas other studies did not (12,23). Importantly, in vivo, the extent of neutral lipid transfer is highly dependent upon the concentration and composition of the endogenous substrate and donor particles (24), as reflected by the inverse relation between postprandial triglycerides and postprandial HDL cholesterol in the present study.

Whether CETP is atherogenic or anti-atherogenic is subject of intense debate (25). 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 (26). In this respect, we earlier demonstrated that CETP concentration was related to cardiovascular disease in postmenopausal women with T2DM, who have elevated levels of triglycerides as compared to women without T2DM (27). The present results stress the role of diet in the potential atherogenicity of CETP.

**Effect of statin treatment on postprandial lipid metabolism**

The decrease in HDL cholesterol after the fat-rich meal in the T2DM-ST study group did not differ from the decrease in diabetic patients who did not use statin medication. This is in agreement with a study in patients with the metabolic syndrome showing a decrease in HDL cholesterol levels which was independent of lipid lowering therapy (8). The decrease in HDL cholesterol in the T2DM-ST group was, however, less as compared to the healthy women. Furthermore, statins reduce plasma CETP concentration by acting on CETP gene expression in the liver due to inhibition of cholesterol synthesis (28). Indeed, in the present study, the patients with T2DM who were treated with statins showed a lower fasting CETP concentration in comparison with the T2DM patients who were not treated with statins and with healthy women. However, we demonstrated that the effect of statins on CETP and postprandial HDL cholesterol had no consequences for the relation between both parameters.
The postprandial increase in CETP concentration is in line with two previous studies in normolipidemic subjects following an oral liquid fat-load (22) and after a fat-rich meal in hypercholesterolemic women (23). However, other investigators showed no significant postprandial increase in CETP concentration in T2DM patients or in healthy controls, which may be due to the limited number of subjects (12). The current study also showed, that the postprandial increase in plasma CETP concentration was similar among healthy individuals, patients with T2DM and patients with T2DM who use statin medication. So it is unlikely that the baseline plasma lipid and/or glucose concentrations determine the increment in plasma CETP concentration.

The rise of CETP may be the result of increased cellular secretion of CETP by liver- or adipose tissue stores since CETP is known to be regulated by post-translational mechanisms (29). However, Radeau et al. demonstrated a close correlation between adipose tissue CETP mRNA abundance and plasma CETP concentrations (r=0.85) (30), 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.

Strengths and limitations of the study

Strengths of the present study are the relatively large number of persons studied and the application of fat-rich and carbohydrate-rich meals demonstrating the effects of a fat-rich meals in comparison with low-fat meals. A limitation is that only post-menopausal women were investigated. Caution should therefore be exercised in extrapolating the present data to effects in men and premenopausal women, especially since it has been reported that CETP gene expression is influenced by sex hormones (29).

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 cholesterol concentration. Fasting CETP levels and postprandial changes in triglyceride levels are both inversely and independently related to these changes in HDL cholesterol observed after fat-rich meals. Plasma CETP concentration may contribute to the postprandial atherogenic lipoprotein profile in postmenopausal women by decreasing HDL cholesterol levels.

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### REFERENCES


12. Lottenberg SA, Lottenberg AM, Nunes VS, McPherson R, Quintao EC 1996 Plasma cholesteryl ester transfer protein concentration, high-density lipoprotein cholesterol esterification and transfer rates to lighter density lipoproteins in the fasting state and after a test meal are similar in Type II diabetics and normal controls. Atherosclerosis 127: 81-90


18. Voorlichtingsbureau voor de Voeding. NEVO Table Netherlands (Dutch Nutrient Database). 2001. (GENERIC) Ref Type: Serial (Book,Monograph)
25. Tall AR, Yvan-Charvet L, Wang N 200 The failure of torcetrapib: was it the molecule or the mechanism? Arterioscler. Thromb. Vasc. Biol. 27: 257-260
29. Tall AR 1993 Plasma cholesteryl ester transfer protein. J.Lipid Res. 34: 1255-1274