

Diet Modulates Plasma Neutral Lipid Transfer Protein Activity in Normolipidemic Human Subjects

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Lipid transfer proteins (CETP) are instrumental in the distribution of neutral lipids and phospholipids over the lipoproteins in human plasma and therefore affect lipoprotein metabolism [1, 2]. Although the function of CETP has been partially identified, little is known about the regulation of CETP activity in human plasma. The activity of CETP is increased in hypercholesterolemic, dysbetalipoproteinemic, and diabetic subjects, all situations in which (VLDL+LDL) cholesterol levels are increased [3–5]. Diet-induced alterations in CETP activity have been reported in hyperlipidemic men and in rabbits [6–8]. Also in these conditions the increase/decrease in CETP activity parallels the increase/decrease in plasma cholesterol. All studies mentioned above deal with hyperlipidemic situations. We therefore performed studies to investigate the effect of diets on the CETP activity in plasma of normolipidemic subjects. 22 males and 30 females (aged 19 to 48 yrs, plasma total cholesterol: 4.8 ± 0.7 mM, plasma triglycerides: 1.0 ± 0.6 mM, HDL-cholesterol: 1.3 ± 0.3 mM) were placed on a diet rich in saturated fat ("sat-diet": 19.3 en.% saturated fat, 11.5 en.% monounsaturated fat, and 4.6 en.% polyunsaturated fat) for 17 days (baseline period). The next 36 days the subjects received a diet rich in olive oil ("mono-diet": 12.9 en.% saturated fat, 15.1 en.% monounsaturated fat, and 7.9 en.% polyunsaturated fat) or rich in sunflower oil ("poly-diet": 12.6 en.% saturated fat, 10.8 en.% monounsaturated fat, and 12.7 en.% polyunsaturated fat) (test periods). All diets were equal with respect to the relative amounts of carbohydrate (49 en.%), protein (13 en.%), and fat (37 en.%) [9]. The CETP activity was measured, using a method independent of endogenous lipoproteins, as the rate of exchange of radioactive cholesteryl ester between labelled LDL and unlabelled HDL [10]. The activity of CETP is expressed as nmoles of CE transferred/h/ml plasma, the value obtained is dependent on the incubation conditions.

CETP activity ranged from 68 to 155 nmoles CE transferred/h/ml plasma, with a mean of 113 ± 22 nmoles CE transferred/h/ml plasma. In the "mono-diet" group CETP activity was significantly decreased (102 ± 19 vs 115 ± 20 ; $p < 0.001$).

The decrease in CETP activity in the "poly-diet" group was not significant (107 ± 22 vs 111 ± 23). To exclude any effect of the time period between the baseline and the test period we compared the effects of the "mono-diet" and "poly-diet" directly. CETP activity falls by $10.2 \pm 10.4\%$ on the "mono-diet" and by $3.1 \pm 11.9\%$ on the "poly-diet" (95% confidence interval for the difference between the effects of the 2 diets, -14.3% to -1.8%). Plasma total cholesterol decreased from 5.19 ± 0.93 mM to 4.54 ± 0.89 mM in the "mono-diet" group ($p < 0.001$) and from 5.09 ± 0.71 mM to 4.65 ± 0.72 mM in the "poly-diet" ($p < 0.001$). HDL cholesterol did not change significantly. More detailed information on these changes in plasma lipoproteins is presented elsewhere [10].

Comparing the response of CETP and the response of various plasma lipid levels to the

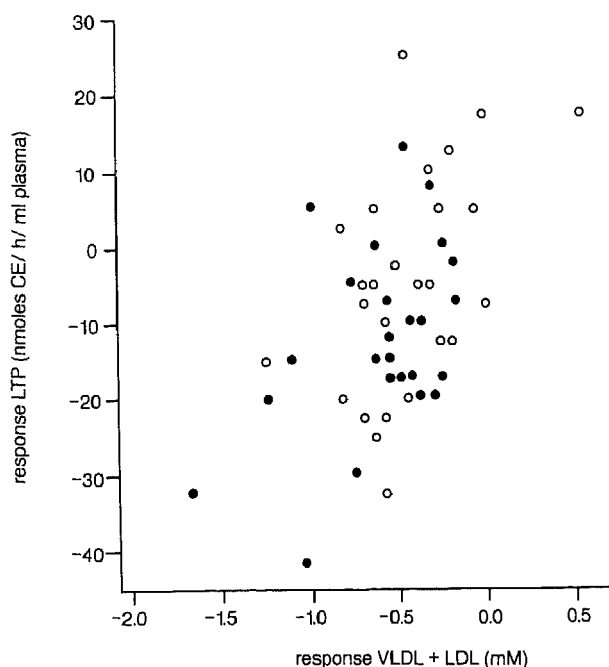


Fig. 1. Relationship between CETP-response and (VLDL+LDL) response in the "mono-diet" group ($r=0.471$, $p < 0.02$) and the "poly-diet" group ($r=0.509$, $p < 0.01$). Pearson correlation coefficient (r) for all subjects is 0.523 ($p < 0.0001$). ●: "mono-diet", ○: "poly-diet"

different diets, positive correlations were found between changes in CETP activity and changes in (VLDL+LDL) cholesterol and total plasma cholesterol. In Fig. 1 the changes in CETP are plotted against changes in (VLDL+LDL) cholesterol.

This study shows that diet can affect CETP activity in normolipidemic subjects. Of interest for the metabolic regulation of CETP activity is that the decrease in CETP activity parallels the decrease in total plasma cholesterol and (VLDL+LDL) cholesterol. It is difficult to assess whether the correlation of changes in (VLDL+LDL) with changes in CETP activity points to a causal relationship. Since different situations of hypercholesterolemia lead to an increase in CETP activity, it is tempting to propose that CETP activity is regulated by the level of (VLDL+LDL) cholesterol.

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Triglycerides and Atherosclerosis

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Transport and distribution of triglycerides throughout the organism is one of the major functions of plasma lipoproteins. An important means of regulating the delivery of triglycerides to various tissues is through a rate limiting hydrolyses step catalyzed by lipoprotein lipase [1-4]. Both an increased influx of triglycerides rich lipoproteins and a decreased efflux of triglycerides from plasma compartment has been identified as pathophysiologic mechanisms leading to hypertriglyceridemia. The ratio CII/CIII may affect the clearance of triglycerides rich lipoproteins [5].

Zilversmith has made a persuasive cause for the possible importance of chylomicrons degradation products "remnants" in atherogenesis [6-8]. Clinical and epidemiological data suggest that high levels of very low density lipoproteins (VLDL) are associated with increased atherogenic risk, although the point is argued [9]. We studied this problem in Portugal, where type IV is the most frequent dislipoproteinemia.

Results

1) Epidemiologic Data

A) Opportunist Screening

% Frequency	V	II b	II a	Normal
Rural	0	5.3	4.0	59.9
Urbano	0	22.0	23.7	71.9
Laboratory	0	13.7	69.8	11.0

[10]

B) Selective Screening

% Frequency	↑ CT	↑ TG	Normal
Doctors	15.8	11.7	72.5
General population	4.6	20.7	74.7
Newborns	0.0	5.3	94.7

[11]