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# HOMA-IR and non-HDL-C as predictors of high cholesteryl ester transfer protein activity in patients at risk for type 2 diabetes

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ABSTRACT

**Background and aims:** Metabolic syndrome (MS) and type 2 diabetes are highly associated with an abnormal lipoprotein profile, which may be generated and accentuated by high cholesteryl ester transfer protein (CETP) activity. Given the difficulty in measuring CETP activity, the aim was to identify simple biochemical predictors of high CETP activity.

**Design and methods:** Eighty five subjects at risk for type 2 diabetes were classified according to the presence of MS. Lipoprotein profile, HOMA-IR and endogenous CETP activity were evaluated.

**Results:** As expected, MS patients presented higher concentration of glucose, insulin, triglycerides and non-HDL-C and lower HDL-C levels. Moreover, MS patients exhibited increased HOMA-IR and CETP activity. Employing a ROC curve for MS, high CETP activity was defined as $>250\%\,ml^{-1}\,h^{-1}$. The predictive variables of high CETP were non-HDL-C $\geq$ 160 mg/dl (OR = 11.1;95%IC = 3.3–38.2;$p<0.001$) and HOMA-IR > 2.1 (OR = 4.4;95%IC = 1.3–14.8;$p<0.05$).

**Conclusions:** High non-HDL-C and insulin resistance were predictors for increased CETP activity which measurement is not accessible for clinical laboratories.



## 1. Introduction

Metabolic syndrome (MS) and, particularly, type 2 diabetes are generally accompanied by high triglycerides (TG), low high density lipoprotein cholesterol (HDL-C) and increased small and dense-low density lipoprotein (LDL), all of them related to insulin resistance and high risk of cardiovascular disease. This so called "atherogenic dyslipemia" is primarily generated by hepatic VLDL overproduction and may be accentuated by high cholesteryl ester transfer protein (CETP), which mediates the transfer of TG from TG-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters [1,2]. It is important to note that when hypertriglyceridemia is present, CETP induces modifications in lipoprotein chemical composition, increasing the atherogenic properties of apo B-containing lipoproteins and impairing HDL antiatherogenic capacities [3–5]. In fact, in previous studies carried out both in hypertriglyceridemic and MS patients, we found that high CETP specific activity was associated with an increase in proatherogenic factors and a decrease in HDL levels and antiatherogenic functions [6–8]. Furthermore, in patients with non-alcoholic fatty liver disease [9] and even in normotriglyceridemic type 2 diabetic patients [10,11], high CETP activity was associated to an increased prevalence of small and dense LDL particles. Based on this putative proatherogenic role of CETP, its inhibition by pharmacological agents has been proposed as a strategy to reduce cardiovascular disease [12]. Several studies carried out in small groups of patients consistently reported an increase in HDL-C levels of approximately 30–50%, but still failed to demonstrate favourable results regarding cardiovascular disease events [13]. In any case, it would be essential to measure or to estimate CETP activity, in order to ensure CETP inhibitory treatment.

Insulin resistant-associated conditions are a worldwide major disorder. The prevalence of MS in USA, employing the diagnostic criteria of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) [14], was reported to be over 24% [15,16]. In Latin America, the Cardiovascular Risk Factor Multiple Evaluation in Latin America Study (CARMELA) reported results ranging from 15 to 27% [17] and, in particular, in Buenos Aires, Argentina, it was 27 and 18% for adult men and women, respectively. Using the definition of the International Diabetes Federation (IDF) [18], this prevalence was still higher. Actually, in a previous study, we observed that the prevalence of MS screened among workers with 40 to 65 years was 39.3% in men and 29.0% in women [19]. Therefore, considering that CETP influences the risk of cardiovascular disease, evaluation of CETP activity would provide useful information of clinical relevance. Particularly, in individuals at significant risk for development of type 2 diabetes, it has been consistently and extensively reported that increased CETP activity further enhances cardiovascular disease risk, thus making these

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patients eligible for CETP inhibitory therapy. However, measurement of CETP activity requires complex techniques which are not easily standardized and automatized [20], thus limiting their implementation in clinical laboratories.

Considering that high CETP activity might identify subjects with increased risk of cardiovascular disease, the main aim of the present study was to identify biochemical predictors of high CETP activity commonly measured in clinical practice by standardized and precise methods in an Argentinean cohort of subjects at risk for type 2 diabetes.

## 2. Methods

### 2.1. Subjects

All subjects were inhabitants of the city of Viedma, Rio Negro, Argentina. Subjects at risk for type 2 diabetes were identified as those individuals who were older than 45 years and presented one or more of the following risk factors: a) being overweight (BMI > 25 kg/m$^2$), b) first-degree relative with diabetes, c) hypertension, d) history of gestational diabetes, and e) physical inactivity, in accordance with ADA statement [21]. Subjects who matched any of the following criteria were excluded: a) personal history of cardiovascular disease (arteriosclerosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, shock, endocarditis, diseases of the aorta and its branches, disorders of the peripheral vascular system, or congenital heart disease), b) hypothyroidism, c) renal diseases, and d) current therapy with oral contraceptive pills or drugs known to affect glucose or lipid metabolism. The study population comprising 223 individuals was surveyed and blood samples were drawn for biochemical determinations. After categorizing the subjects according to the presence of MS by the IDF definition [18], a random sub-sample of 49 patients from the MS group was selected for CETP activity assessment and compared to an age and sex-matched group of 36 individuals without MS. Informed consent was obtained from all participants and the protocol was approved by the Ethical Committee from Integral Clinical Biochemistry Institute according to the Declaration of Helsinki.

### 2.2. Clinical and anthropometric measurements

Age, presence of familial history of cardiovascular disease or diabetes and smoking status were recorded during a face-to-face interview employing questionnaires previously described [19]. Weight and height were recorded with the subject without shoes and wearing light clothes. Body mass index (BMI) was calculated. Waist circumference was measured at the level of the umbilicus without clothing. Blood pressure was determined after the subject was seated at rest for five minutes employing a mercury sphygmomanometer previously calibrated. Two determinations were taken for each subject and the average between both was used. Every determination was carried out by the same physician.

### 2.3. Biochemical determinations

Blood samples were obtained from the 223 subjects after a 12-hour overnight fast for biochemical determinations. Glucose levels and lipoprotein profile were assessed by standardized techniques (Wiener-Lab, Argentina) in a Technicon RA-1000 analyzer. Plasma insulin levels were measured by an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Homeostasis model assessment for insulin resistance (HOMA-IR) was employed as a surrogate measurement of *in vivo* insulin resistance. The following equation for HOMA-IR index was used: fasting (insulin (μU/ml) x fasting glucose (mmol/l))/22.5. Insulin resistance was defined as HOMA-IR > 2.1, which was the value that best described MS patients in a ROC curve analysis from the 223 subjects at risk for development of type 2 diabetes. Serum samples from the 49 individuals with MS and from 36 sex- and age-matched controls were frozen and stored at −70 °C for determination of CETP activity.

### 2.4. CETP activity

CETP activity was determined in serum samples employing an endogenous assay previously described by Lagrost et al. [20]. Briefly, the ability of serum to promote the transfer of tritiated cholesteryl esters from a tracer amount of biosynthetically labelled $HDL_3$ ($^3$H-CE-$HDL_3$) (NEN Life Science Products, Boston, USA) towards serum apo B-containing lipoproteins was evaluated. Samples (75 μl of serum) were incubated with $^3$H-CE-$HDL_3$ (50 μmol/l cholesterol) and 1.5 mmol/l iodoacetate for 3 h, at 37 °C (final volume = 150 μl). After incubation, apo B-containing lipoproteins were separated by selective precipitation method employing 0.44 mmol/l phosphotungstic acid in the presence of magnesium ions. Radioactivity was measured in the incubation mixture and in the supernatant containing the HDL fraction in a liquid scintillation analyser (Packard 210TR; Packard Instruments, Meridian, CT). Results were expressed as percentage of $^3$H-cholesteryl esters transferred from $HDL_3$ to apo B-containing lipoproteins, per ml, per hour. Incubations were carried out by duplicate, as well as internal controls and blanks were also assayed. Measurements were all carried out within the same assay. Intra-run variation coefficient (CV) was 4.9%.

### 2.5. Data and statistical analysis

Data distribution was tested by Shapiro-Wilks method. Parameters were presented as the mean ± standard deviation and Student parametric test (*T* test) and Mann–Whitney non-parametric test (*U* test) were used to compare the groups. Chi square test was used to compare proportions. The associations of different metabolic variables with CETP activity were assessed using Spearman correlation test and stepwise multiple linear regression. Linear regression model included CETP activity as dependent variable and age, sex, smoking status, levels of non-HDL-C, TG, and HOMA-IR as independent variables. Skewed variables were log transformed before entering the regression models. To analyze the predictive value of independent variables over CETP activity, logistic regression was employed. The cut off point of CETP activity considered for this analysis was obtained by a receiver-operator curve (ROC). Parameters included in the model were age, sex, abdominal obesity according to IDF criteria, TG ≥ 150 mg/dl, non-HDL-C ≥ 160 mg/dl (cut-off point employed according with ATP III guides, for subjects at risk for type 2 diabetes [14]) and HOMA-IR > 2.1. Analyses were carried out using the SPSS (Chicago, IL) statistical software package SPSS version 11.5®.

## 3. Results

Table 1 presents clinical and biochemical characteristics from the 86 patients at risk for type 2 diabetes selected for CETP activity measurement classified according to the presence of MS. Patients with and without MS were similar in age, sex distribution and percentage of smokers. As expected, MS patients had higher BMI, waist circumference, and diastolic and systolic blood pressure. It is worthy to note that the percentage of subjects with familial history of cardiovascular disease and diabetes in the MS group was significantly higher than in the other group.

Regarding the biochemical characteristics, coherent with the close association between MS and insulin resistance, MS patients exhibited higher glucose and insulin plasma levels, in addition to increased HOMA-IR. The prevalence of subjects with impaired fasting glucose was significantly higher in the MS group than among subjects without MS (42.9% *vs.* 8.3%, respectively; $p < 0.001$).

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**Table 1**
Clinical and biochemical characteristics from MS patients and control subjects.

| | MS patients | Control subjects |
|---|---|---|
| N | 49 | 36 |
| Age (years) | 55 ± 8 | 55 ± 8 |
| Sex (male/female) | 14/35 | 12/24 |
| BMI (Kg/m$^2$) | 33.8 ± 7.2 | 26.3 ± 3.6[a] |
| Waist circumference (cm) | 105 ± 17 | 89 ± 8[a] |
| DBP (mmHg) | 90 ± 13 | 81 ± 12[a] |
| SBP (mmHg) | 144 ± 22 | 128 ± 21[c] |
| Smokers (%) | 25.0 | 25.0 |
| Familial history of CVD (%) | 32.7 | 11.1[d] |
| Familial history of diabetes (%) | 38.8 | 13.9[d] |
| Glucose (mg/dl) | 106 ± 35 | 88 ± 12[b] |
| Insulin (mU/l) | 17.6 ± 10.6 | 5.7 ± 2.6[a] |
| HOMA-IR | 4.5 ± 3.1 | 1.3 ± 0.6[a] |
| TG (mg/dl) | 206 ± 117 | 112 ± 51[a] |
| TC (mg/dl) | 215 ± 41 | 200 ± 31 |
| LDL-C (mg/dl) | 136 ± 28 | 127 ± 22 |
| HDL-C (mg/dl) | 44 ± 5 | 53 ± 11[b] |
| Non-HDL-C (mg/dl) | 170 ± 39 | 147 ± 29[b] |
| CETP activity (%/ml.h) | 261 ± 38 | 241 ± 42 [a] |

MS, metabolic syndrome; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; CETP, cholesteryl ester transfer protein.
[a] $p<0.001$.
[b] $p<0.005$.
[c] $p<0.01$.
[d] $p<0.05$.

Furthermore, MS patients also displayed higher concentration of TG and non-HDL-C, as well as lower HDL-C levels than subjects without MS. As it was expected, CETP activity was also significantly increased in MS patients (Table 1). In order to establish a cut-off point for CETP activity, a ROC curve was plotted for patients with and without MS (Fig. 1). High CETP activity was defined as a value over 250% ml$^{-1}$ h$^{-1}$ (area under ROC curve = 0.74; CI95% = 0.64–0.85; $p<0.001$) (Fig. 1).

In the studied population, CETP activity age and sex-adjusted correlations were positive with BMI ($r=0.25$; $p<0.05$), waist circumference ($r=0.29$; $p<0.01$), plasma levels of glucose ($r=0.25$; $p<0.05$), insulin ($r=0.31$; $p<0.005$), TG ($r=0.59$; $p<0.001$), non-HDL-C ($r=0.71$, $p<0.001$), and HOMA-IR ($r=0.35$, $p<0.001$), while negatively associated with HDL-C concentration ($r=-0.33$, $p<0.005$). Regarding the factors that have a bearing on the variations of CETP endogenous activity, the concentration of cholesteryl ester acceptor lipoproteins was found as the most significant one. Multiple linear regression analysis identified non-HDL-C ($B=0.22$,$p<0.001$) and TG ($B=0.06$,$p<0.001$) as the variables most closely associated to CETP activity ($r^2=0.56$, $p<0.001$).

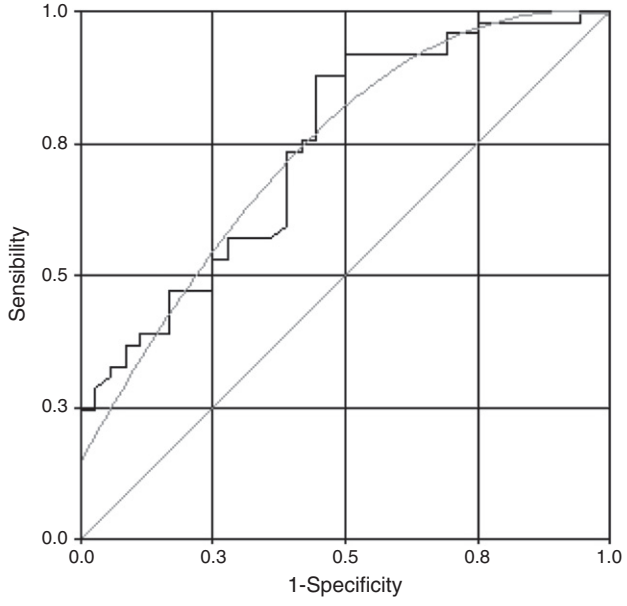


**Fig. 1.** ROC curve showing the sensitivity and specificity to establish a CETP activity cut-off point for patients with and without MS (area under ROC curve = 0.74; CI95% = 0.64–0.85; $p<0.001$).

**Table 2**
Multiple logistic regression analysis of the association between high CETP activity and selected independent variables.

| Variable | OR | 95% CI | p |
|---|---|---|---|
| Sex | 2.0 | 0.60–6.96 | 0.256 |
| Central obesity | 0.31 | 0.07–1.46 | 0.137 |
| HOMA-IR > 2.1 | 4.37 | 1.29–14.83 | 0.018 |
| TG ≥ 150 mg/dl | 0.84 | 0.25–2.87 | 0.837 |
| Non-HDL-C ≥ 160 mg/dl | 11.14 | 3.25–38.15 | 0.0001 |

Dependent variable: CETP > 250%/ml.h.
Central obesity was defined according to sex per IDF criteria.
CETP, cholesteryl ester transfer protein; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; non-HDL-C, non-high density lipoprotein-cholesterol.

Then, to identify predictors of high CETP activity (> 250% ml$^{-1}$ h$^{-1}$), a logistic regression model which included age, sex, abdominal obesity according to IDF criteria, TG ≥ 150 mg/dl, non-HDL-C ≥ 160 mg/dl and HOMA-IR > 2.1 was employed. In this analysis, the significant predictive variables for high CETP activity were non-HDL-C ≥ 160 mg/dl and HOMA-IR > 2.1 (Table 2). Employing these criteria, the studied subjects with increased CETP activity were identified with 73% specificity and 75% sensibility.

## 4. Discussion

In the present study, the main finding was the identification of simple biochemical parameters as predictors of increased CETP activity in a cohort of subjects at risk for type 2 diabetes. Results showed that high endogenous CETP activity was independently associated with non-HDL-C above 160 mg/dl and HOMA-IR over 2.1, after adjustment for several confounders. The simple and reliable determinations of non-HDL-C and HOMA-IR allowed identifying subjects with high CETP activity, which specific measurement requires complex techniques non-easily standardized.

The strong correlation between CETP activity and non-HDL-C most likely reflects the crucial role played by the concentration of cholesteryl ester acceptor lipoproteins as determinants of endogenous CETP activity. This observation was supported by the linear regression analyses and has been acknowledged in several studies [8,22–24].

CETP activity *in-vivo* is also known to be determined at a genetic level. In this regard, much attention has been paid to the Taq1B polymorphism (B1 and B2 alleles) which does not only modulate CETP activity, but has been also proved to contribute to the presence of diabetes, independently of age, sex, BMI and waist circumference [25].

Given that in the present study an endogenous substrate assay was employed, the measurement of CETP activity resembles the *in-vivo* situation since plasma CETP activity is influenced by both triglyceride rich-lipoproteins and CETP plasma concentrations. In contrast, exogenous CETP activity assays are only an indirect measure of CETP concentration [20,26].

On the other hand, insulin resistance was estimated as HOMA-IR over 2.1. This cut-off value was calculated in an analysis carried out in the total population (n = 223) using a ROC curve to best describe subjects with MS (data not shown). It is possible that the relative low cut-off value obtained in comparison to other studies carried

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out in Argentinean population, in which HOMA-IR ranged from 2.7 to 3.1 [19,27], could be attributed to the fact that the subjects enrolled in this study were at high risk for type 2 diabetes and older than 45 years.

Similar to previous studies, CETP activity correlated positively with BMI, waist circumference, TG, non-HDL-C, glucose, insulin and HOMA-IR, while negatively with HDL-C [8,22,23]. In particular, waist circumference presented a slightly stronger association with CETP activity than BMI. Noteworthy, general and abdominal adiposity were proposed to be closely related to CETP activity in other studies, as adipose tissue might contribute to CETP plasma concentration [28]. However, this association resulted not significant in the multivariate regression analyses. Much likely, this result might be consequence of the intimate association that HOMA-IR displays with BMI and waist circumference, thus being HOMA-IR a stronger predictor of high CETP activity than general or abdominal adiposity.

Whether CETP is proatherogenic or antiatherogenic is still under debate [22,29–32]. Though prospective investigations in general population or in patients under statin-treatment showed that individuals with low CETP exogenous activity or concentration experienced higher cardiovascular disease incidence [32–34], Kappelle et al. and Zeller et al. [22,35] observed that high CETP endogenous activity was associated with CVD incidence and the occurrence of the first myocardial infarction at a younger age, respectively. This point suggests that the observed controversy might be attributed to the type of assay employed to measure CETP activity and/or to additional factors, such as hypertriglyceridemia or statin treatment [22,29–31]. In the present study and in agreement with previous studies carried out in hypertriglyceridemic and MS patients [6–8], high CETP activity was associated with an increase in proatherogenic factors and a decrease in HDL levels, thus supporting CETP proatherogenic role in subjects at risk for type 2 diabetes.

Potential mechanisms responsible for the association between high CETP activity and increased risk of cardiovascular disease are the generation of the highly atherogenic small and dense LDL particles [9,36] and the formation of triglyceride-enriched HDL subfractions, known to be less efficient in their antiatherogenic capacities [3–8]. Thus, targeting CETP for its inhibition has been proposed as one of the novel therapies for patients characterized by increased TG and low HDL-C concentrations [37].

In conclusion, in patients at risk for type 2 diabetes, insulin resistance, detected through high HOMA-IR, and increased levels of apo B-containing lipoproteins, estimated through elevated non-HDL-C, are independent predictors of increased CETP activity, which measurement may not be carried out in clinical laboratories employing easily standardized and precise methods.

## Conflict of interest

The authors declare to have no conflicts of interest.

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