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Cardiovascular risk in patients with rheumatoid arthritis: the role of cholesterylester transfer protein

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Original Article

Cardiovascular risk in patients with rheumatoid arthritis: the role of cholesterylester transfer protein

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Abstract

Aim

To detect serum level of cholesterylester transfer protein (CETP) (the enzyme involved in reverse cholesterol transport) in patients with rheumatoid arthritis (RA) and to evaluate its relation to various clinical parameters of the disease, lipid profile, and carotid intima-media thickness (CIMT) as a marker of atherosclerosis and cardiovascular disease risk.

Patients and methods

This study involved a total of 80 participants, comprising 50 patients with RA and 30 age-matched and sex-matched healthy controls. Detailed medical history and thorough clinical examination (general and musculoskeletal) as well as laboratory investigations including lipid profile were performed for all patients with RA. Serum level of CETP was assessed by enzyme-linked immunosorbent assay technique. Carotid ultrasound scan was performed for all patients with RA to detect CIMT.

Results

Serum level of CETP was significantly lower in patients with RA than controls (4.11 ± 2.77 ng/ml in patients with RA and 5.30 ± 2.73 ng/ml in controls, $P = 0.003$). Regarding lipid profile values, high-density lipoprotein was lower in patients with RA relative to controls (63.02 ± 12.8 vs. 69.8 ± 6.7 mg/dl, $P = 0.012$), whereas total cholesterol (218.9 ± 39.5 vs. 206.9 ± 31.8 mg/dl, $P = 0.073$), triglycerides (144.2 ± 16.2 vs. 136.1 ± 16.6 mg/dl, $P = 0.059$), and low-density lipoprotein (118.5 ± 27.5 vs. 112.6 ± 38.5 mg/dl, $P = 0.56$) showed no significant differences between both groups. No correlation was found between serum level of CETP and the characteristics of patients with RA including demographic data, disease activity markers (28-joint disease activity score, erythrocyte sedimentation rate, and C-reactive protein), serological markers (rheumatoid factor and anti-cyclic citrullinated peptide antibodies titer), as well as lipid profile parameters. On the contrary, serum level of CETP was significantly negatively correlated with CIMT (r=−0.321, $P = 0.023$).

Conclusion

Finally, we concluded that CETP was found to be low in patients with RA when compared with controls and is inversely related to CIMT, suggesting its possible role in cardiovascular mortality risk in this disease.

Keywords: Cardiovascular risk, cholesterylester transfer protein, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting ~ 1% of the adult population with core manifestations involving synovial joints together with other comorbidities including accelerated atherosclerosis and cardiovascular disease (CVD) with increased mortality rate. The risk for CVD represents an interplay between traditional and nontraditional cardiovascular risk factors with altered lipid metabolism, and endothelial inflammation play an important role [1]. In RA, there is reduction of cardio-protective high-density lipoprotein (HDL), besides altered metabolism of other lipoproteins that represents 'proatherogenic characteristics' [2]. Chronic inflammation that involves multiple inflammatory

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cytokines such as interleukin 1 and 6 and tumor necrosis factor alpha may play a role in dyslipidemia of RA [3].

Cholesterylester transfer protein (CETP), also called plasma lipid transfer protein, is a plasma protein that mediates the transfer of cholesterylesters and triglycerides between different lipoproteins. It transports triglycerides from very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL) and exchanges them for cholesterylesters from HDL, resulting in formation of cholesterylester-enriched VLDL and LDL and reduction of HDL-C [4]. As a result, several therapeutic agents have been designed to inhibit the CETP aiming to increase the level of HDL; however, these agents failed to gain the target and paradoxically showed increase in CVD risk [5]. Other studies reported that lower CETP activity possesses a greater CVD risk [6]. Thus, the effect of CETP on lipid metabolism and its role in CVD is not fully understood and needs to be further investigated.

The aim of the study was to detect serum level of CETP in patients with RA and to evaluate its relation to various clinical parameters of the disease, lipid profile, and carotid intima-media thickness (CIMT) as a marker of atherosclerosis and CVD risk.

Patients and methods

This cross-sectional study involved 80 participants, comprising 50 patients with RA [diagnosed according to American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) revised criteria][7] and 30 age-matched and sex-matched healthy controls. This study comprised patients with RA aged above 18 years, who had disease duration more than or equal to 1 year, and were not on glucocorticoid therapy for the past 3 months. The following patients were excluded from the study: patients who received anti-tumor necrosis factor alpha treatment or other biologic therapies and patients with a current history of angina, myocardial infarction, stroke, diabetes mellitus, chronic hypertension, cancer, hypothyroidism, Cushing syndrome, severe renal or liver diseases, current infection, or any chronic disorders including other autoimmune diseases. Patients on statin therapy; women on contraceptive pills; pregnant, lactating, and postmenopausal women; obese patients (BMI >30); and smokers were also excluded from the study. The exclusion criteria were applied on the control group.

Written consent was obtained from the patients and controls after explanation of all the details of the study.

This study was approved by the ethics committee of General Organization of Teaching Hospitals and Institutes and conducted according to the guidelines of Helsinki Declaration (2000).

Detailed medical history and thorough clinical examination (general and musculoskeletal) were performed for all patients with RA. Disease activity was assessed using 28-joint disease activity score (DAS28) [8]. Both groups of the study were subjected to full investigations, including C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP antibodies), complete blood count, total cholesterol, triglycerides, HDL, LDL, in addition to serum level of CETP. Carotid ultrasound scan was performed for all patients with RA to detect CIMT.

Carotid ultrasound scan

Ultrasonography was performed using a GE heathcare (Chicago, Illinois, USA) Vivid 7 system equipped with a 13-MHz linear array imaging probe. The right common carotid artery was used for examination. The patient lied in a supine position, while the head tilted away from the examined side, and the neck slightly extended. The transducer was applied so as the near and far walls of the common carotid artery being parallel to the transducer footprint, and the lumen diameter was determined in the longitudinal plane. At a certain point located one cm proximal to the carotid bifurcation, the intima-media thickness (IMT) of the far wall was determined as the distance between 'the media–adventitia interface' and 'the lumen–intima interface.' The IMT was measured for successive four sites at 1-mm intervals, and the average of the four measurements was used for assessment. All measurements were performed by investigators without knowledge about the patients' clinical data. Upper normal average IMT was estimated to be up to 0.8 mm with atherosclerotic plaque defined as a thickness more than 1.5 mm as measured from 'the media–adventia interface' to 'the intima–lumen interface' [9].

Laboratory investigations

Fasting blood samples (5 ml) were taken by venipuncture from each individual. Two milliliters was used for the measurement of erythrocyte sedimentation rate, and the last 3 ml was allowed to coagulate for 30 min at room temperature. Subsequently serum was separated by centrifugation for 10 min at 3000 rpm and stored at −70ºC until biochemical analysis was performed.

Lipid profile tests, which included serum cholesterol, triglycerides, HDL, and LDL, were measured by using the vitro System 350 (Ortho Clinical Diagnostics, Raritan, New Jersey, USA). CRP and RF were measured by the use of enzyme-linked immunosorbent assay (ELISA) kits provided by DRG (USA) and IBL International (Hamburg, Germany), respectively, following the manufacturer's instructions.

Highly purified anti-CCP (vimentin) antibodies were measured by indirect ELISA by a commercially available kit from organic diagnostic GmbH – Germany.

Assessment of cholesterylester transfer protein

Human serum CETP was determined by ELISA (Kit from EIAab, China). In this assay, the microtiter plate has been pre-coated with an antibody specific to CETP. Standards or samples were added to the microtiter plate wells that contain biotin-conjugated antibodies preparation specific for CETP, and then avidin conjugated to horseradish peroxidase was added to each well. Only those wells that contain CETP, biotin-conjugated antibody, and enzyme-conjugated avidin exhibited a change in

color. The enzyme-substrate reaction was terminated by the addition of sulfuric acid solution, and the color change was measured at a wavelength of 450 ± 2 nm. The concentration of CETP in the samples was determined by comparing the optical density of the samples to the standard curve [10].

Statistical analysis

The collected data were tabulated and analyzed using SPSS, version 16 software (SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages, and Fisher's exact test was used for their analysis. Continuous variables were tested for normality using Shapiro–Wilk test, assuming normality at *P* value more than 0.05. They were expressed as mean ± SD and range, and analysis was done using Mann–Whitney *U* test and Spearman's correlation coefficient.

The accepted level of significance in this work was stated at 0.05. *P* value less than 0.05 was considered significant.
P value more than 0.05 is nonsignificant (NS).
P value less than 0.05 is significant (S).
P value less than or equal to 0.001 is highly significant (HS).

Results

This study included 50 patients with RA, comprising eight (16.0%) males and 42 (84.0%) females. Their ages ranged from 21 to 49 years (mean ± SD, 35.1 ± 13.6), whereas the duration of the disease was from 2 to 15 years (mean ± SD, 7 ± 3). Moreover, 30 age-matched and sex-matched healthy persons were also included in the study as a control group. All patients with RA were seropositive for RF (except one patient) and anti-CCP antibodies tests. Their DAS28 score ranged from 1.36 to 8.11 (mean ± SD, 3.83 ± 1.3) and CIMT ranged from 0.39 to 1.2 mm (mean ± SD, 0.9 ± 0.17) (Table 1).

Both study groups were compared regarding inflammatory marker (CRP), lipid profile, and CETP. CRP was found to be higher in patients with RA than controls (mean ± SD, 22.9 ± 9.41 mg/l in RA vs. 1.80 ± 0.54 mg/l in controls, $P < 0.001$). Serum level of CETP was significantly lower in patients with RA than controls (mean ± SD, 4.11 ± 2.77 ng/ml in patients with RA and 5.30 ± 2.73 ng/ml in controls, $P = 0.003$). Regarding lipid profile values, HDL was lower in patients with RA relative to controls (mean ± SD, 63.02 ± 12.8 vs. 69.8 ± 6.7 mg/dl, $P = 0.012$), whereas total cholesterol (mean ± SD, 218.9 ± 39.5 vs. 206.9 ± 31.8 mg/dl, $P = 0.073$), triglycerides (mean ± SD, 144.2 ± 16.2 vs. 136.1 ± 16.6 mg/dl, $P = 0.059$), and LDL (mean ± SD, 118.5 ± 27.5 vs. 112.6 ± 38.5 mg/dl, $P = 0.56$) showed no significant differences between both groups (Table 2).

No correlation was found between serum level of CETP and the characteristics of patients with RA, including demographic data, disease activity markers (DAS28, erythrocyte sedimentation rate, and CRP), serological markers (RF anti-CCP antibodies titer), as well as lipid profile parameters. However, there was a significant negative correlation between serum level of CETP and CIMT ($r = -0.321$, $P = 0.023$) (Table 3).

Table 1: Demographic, clinical, laboratory, and radiological characteristics of patients with rheumatoid arthritis group

Variable ($n = 50$)	Mean ± SD	Range
Age (years)	35.1±13.6	21-49
Duration of the disease (years)	7±3	2-15
Sex [*n* (%)]		
Male	8	16.0%
Female	42	84.0%
DAS28	3.83±1.3	1.36-8.11
Grades (total 50)		
0	7	-
I	11	-
II	26	-
III	6	-
RF		
Negative	1	2.0%
Positive	49	98.0%
Anti-CCP Ab		
Positive	50	100%
CIMT (mm)	0.9±0.17	0.39-1.2

Anti-CCP Ab, anti-cyclic citrullinated peptide antibodies; CIMT, carotid intima-media thickness; DAS28, 28-joint disease activity score; RF, rheumatoid factor.

Discussion

Disordered lipid metabolism is one of the determining factor of accelerated atherosclerosis detected in chronic inflammatory diseases such as RA [11]. CETP is responsible for cholesterylester transport between HDL, VLDL, and LDL with subsequent reduction of the size of HDL, which become cholesterol ester poor but triglyceride enriched. This structure makes it capable of effective new cycle of cholesterol removal from peripheral tissues [12].

In the current study, we reviewed the role of CETP as a risk factor for CVD in patients with RA, and we studied its relation to different disease variables (clinical and laboratory). The results showed that serum level of CEPT was lower in patients with RA than controls, which came in agreement with Ferraz-Amaro *et al*. [13], who reported that plasma CETP concentrations as well as CETP activity were also lower in patients with RA, and on studying the relation between the serum level of CETP and clinical or laboratory variables of disease activity, including DAS28 and CRP, no correlation between any of these variables and CETP was found. These results support the reports of the current study but differ from the study of Hernández-Hernández *et al*.[14] who detected negative correlation with CRP.

All patients included in the current study were not on steroid therapy to roll out the possible effects on lipid profile and CETP activity as daily prednisone intake in patients with RA was inversely correlated with serum level and activity of CETP, whereas patients who were glucocorticoid naive showed no differences in either CETP mass or activity when compared with controls [13].

Table 2: Comparing the studied groups regarding laboratory findings

Variables	patients with RA (*n*=50)	Controls (*n*=30)	*Z* of MWU test	*P*
	Mean±SD	Mean±SD		
RF titer (U/l)	126.8±104.4	11.4±2.76	7.45	<0.001 (HS)
Anti-CCP Ab titer (U/ml)	339.6±271.4	15.2±7.1	7.47	<0.001 (HS)
CRP (mg/l)	22.9±9.41	1.80±0.54	7.46	<0.001 (HS)
CETP (ng/ml)	4.11±2.77	5.30±2.73	3.01	0.003 (S)
Total cholesterol (mg/dl)	218.9±39.5	206.9±31.8	1.79	0.073 (NS)
TG (mg/dl)	144.2±16.2	136.1±16.6	0.1.88	0.059 (NS)
HDL (mg/dl)	63.02±12.8	69.8±6.7	2.51	0.012 (S)
LDL (mg/dl)	118.5±27.5	112.6±38.5	0.58	0.56 (NS)

Anti-CCP Ab, anti-cyclic citrullinated peptide antibodies; CETP, cholesterylester transfer protein; CRP, C-reactive protein; HDL, high-density lipoprotein; HS, highly significant; LDL, low-density lipoprotein; MWU, Mann–Whitney U test; NS, nonsignificant; RF, rheumatoid factor; S, significant; TG, triglycerides.

Table 3: Correlation between cholesterylester transfer protein and the studied variables in patients with rheumatoid arthritis

With	CETP	
	Rho	*P*
Age	−0.093	0.52
Duration of the disease	−0.227	0.13
ESR (mm/h)	−0.042	0.77
DAS28	−0.036	0.80
RF titer	0.228	0.11
Anti-CCP Ab	0.227	0.12
CRP	−0.226	0.12
Lipid profile		
TC	0.234	0.102
TG	0.145	0.31
HDL	−0.049	0.74
LDL	0.131	0.37
CIMT (mm)	−0.321	0.023 (S)

Anti-CCP Ab, anti-cyclic citrullinated peptide; CEPT, cholesterylester transfer protein; CIMT, carotid intima-media thickness; CRP, C-reactive protein; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RF, rheumatoid factor; S, significant; TC, total cholesterol; TG, triglycerides.

With respect to either CETP had a role in inflammation or not, several studies were conducted to evaluate its influence on inflammatory response in mice [15]. Human CETP transgenic mice were compared with control mice (wild type, WT) after induced polymicrobial sepsis, to investigate their survival rate and inflammatory profiles. CETP mice showed higher survival rate, decreased toll-like receptor 4 (TLR4), and lower IL-6 plasma concentration, when compared with WT mice. Moreover, when recombinant human CETP was added to WT mice macrophages, they showed decreased lipopolysaccharides uptake, TLR4 expression, IL-6 secretion, and NF-κB activation, suggesting a possible role of CETP in modulation of inflammation [16].

Similar findings were detected by Patricia [17]. There was a decrease in cytokine production, as well as reduction in hepatic expression of TLR4 with CETP-expressing mice. These data suggest the role of CETP in the defense mechanism against an exaggerated production of proinflammatory cytokines.

Atherosclerosis represents the link between cholesterol metabolism and inflammation in multiple disorders such as metabolic syndrome and autoimmune diseases, and this is influenced by interaction between 'cholesterol-laden macrophages' released to the periphery and endothelial cells [11].

Cholesterol is processed in the body via two distinct pathways: the first one involves cholesterol delivery for usage by the peripheral cell and accumulation in adipose tissue [18], whereas the second pathway is termed 'reverse cholesterol transport (RCT),' in which cholesterol is transported from the periphery to liver or other organs using cholesterol for hormonal synthesis such as adrenals and ovaries as well as its excretion into bile and feces [19], and this is mediated by two different mechanisms in humans and animals. In animals, direct way is mediated by scavenger receptor B1, which selectively uptakes cholesterol content from HDL. In human, an indirect mechanism is involved that is mediated by CETP. This mechanism transports cholesterol ester from HDL to VLDL and LDL while taking triglycerides. This processed LDL is removed from the circulation by LDL receptor pathway. Triglycerides loaded onto HDL are not stable and become degraded by hepatic lipase, so HDL is left for a new turn of cholesterol reuptake from cells [20].

During chronic inflammatory response, RCT is suppressed, aiming to increase lipid supply to peripheral tissues to obey their demands to modulate inflammation and to allow for tissue repair[21] The acute-phase reactants can influence RCT by different ways, among them is their suppressive effect on hepatic CETP gene expression in human CETP transgenic mice [22–24].

This effect of acute-phase response on CETP may explain why it is reduced in inflammatory condition like RA.

The inflammatory response also has a characteristic influence on HDL. In the current work, its level in patients with RA was

lower than in controls. Gamboa-Cárdenas *et al*.[25] reported that this decreased level of HDL is closely related to disease activity in patients with RA and can be used as a valuable marker of disease activity.

During inflammation, HDL possesses certain features including loss of its cholesterol efflux capacity[26] as well as its antioxidant activity [27].

This current work aimed to assess the role of CETP as a risk factor for CVD in patients with RA. CETP showed to be inversely related to CIMT parameters, suggesting that its reduction recorded in inflammatory immune response may contribute to CVD.

On the contrary, several studies reported both atherogenic and anti-atherogenic effects of CETP. In its 'proatherogenic role,' it increases cholesterol mass transported by VLDL and LDL, followed by increase cholesterol supply to the peripheral tissues with possibility for retention of oxidized lipid in the arterial wall [28]. This pointed to the concept of the inhibition of CETP as a way of reduction of CVD risk, so several drug trials were conducted on CETP inhibitors like torcetrapib, dalcetrapib, and evacetrapib (which increased HDL cholesterol levels and lowered LDL). However, these clinical trials did not result in lower rate of cardiovascular events [5,29,30]. Anacetrapib, a potent CETP inhibitor, reported greater benefit on coronary event reduction owing to the effects on lowering 'non-HDL cholesterol levels' [31]. These data concluded that CETP inhibition for increasing HDL may not be an optimal strategy to reduce the risk of atherosclerosis so improving HDL function should be tried rather than merely raising HDL level, and this mechanism is more likely to decrease CV events [32]. This refers to another concept related to CETP.

CETP deficiency is associated with CVD events even if HDL level is normal or even high, as shown by several genetic studies conducted on Japanese and Dutch population [33–36]. In other words, HDL-C elevation in case of CETP deficiency may lose its protective effect [37,38].

Other genetic evidences pointed to weakness of CETP inhibition as a tool to reduce CVD risk [39], and this concept was also supported by other community-based studies [6,40–42].

More recently, another work referred to the relationship between CETP levels and heart failure. Negative correlation between CETP and brain natriuretic peptide was detected. So lower CETP levels may be a marker of heart failure aggravation and associated with unfavorable outcome [43].

In our work, CIMT was found to be increased and inversely related to CETP serum level. This comes in agreement with Ferraz-Amaro *et al*. [13], as they demonstrated that lower CETP level is associated with higher SCORE (Systematic Coronary Risk Evaluation) index and more cardiovascular mortality risk.

Related to anti-atherogenic effects of CETP, the only mechanism involved in RCT in human is mediated by CETP, so patients with higher CETP showed significant increase in 'capacity for cholesterol efflux' from 'cholesterol-laden macrophages' when compared with efflux capacity in patients with low CETP. In addition, there was an inverse relation between efflux capacity and CIMT [44].

The role of CETP in RCT was confirmed by previous animal studies that link this role to active LDL receptors. CETP-expressing mice restore RCT ability to normal in absence of scavenger receptor class B type 1, but they cannot when deficient in LDL receptors [45,46].

The relation between CETP, lipid profile parameters, and inflammatory markers was not confirmed in our study. Regarding this issue, several previous studies detected the same reports [13,47–49]. In those studies, CETP was detected by standardized assay. This in-vitro assessment may not necessarily be related closely to its actual in-vivo activity. CETP has been involved in lipid transport reactions among several lipoprotein molecules [50].

Conversely, other studies showed that serum CETP levels were highly correlated with the enzymatic activity ($r = 0.5$, $P = 0.00$), so that serum levels could be enough to express the activity of this enzyme [13,14].

This study confronted some limitations. Owing to cross-sectional design and the small sample size involved in this study, its results cannot be applied to all patients with RA. Therefore, larger prospective studies should be conducted to confirm the predictive value of CETP on CVD risk.

Conclusion

Finally, we concluded that CETP was found to be low in patients with RA when compared with controls and was inversely related to CIMT, suggesting that its low level possibly contributes to the development of CVD in these patients, but larger studies are needed to evaluate its role in prediction of cardiovascular risk.

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Conflicts of interest

There are no conflicts of interest.

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