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Original article

Beneficial effect of CETP gene polymorphism in combination with a Mediterranean diet influencing lipid metabolism in metabolic syndrome patients: CORDIOPREV study

Antonio Garcia-Rios [a, 1], Juan Francisco Alcala-Diaz [a, 1], Francisco Gomez-Delgado [a], Francisco Javier Delgado-Lista [a], Carmen Marin [a], Ana León-Acuña [a], Antonio Camargo [a], Fernando Rodriguez-Cantalejo [b], Ruth Blanco-Rojo [a], Gracia Quintana-Navarro [a], Jose Maria Ordovas [c], Francisco Perez-Jimenez [a], Jose Lopez-Miranda [a, 2], Pablo Perez-Martinez [a, *, 2]

[a] Lipids and Atherosclerosis Unit, IMIBIC/Hospital Universitario Reina Sofía/Universidad de Córdoba and Ciber Fisiopatologia Obesidad y Nutricion, Instituto Salud Carlos III, Spain
[b] Clinical Analysis Service, IMIBIC/Hospital Universitario Reina Sofía/Universidad de Córdoba, Spain
[c] Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University School of Medicine, Boston, MA, USA

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SUMMARY

The cholesteryl ester transfer protein (CETP) gene has been implicated in high-density lipoprotein (HDL-C) metabolism. However, little is known about the impact of this gene on metabolic syndrome (MetS) patients and its interaction with diet. Here, we evaluate whether the consumption of a Mediterranean diet, compared with a Low-fat diet, interacts with the *rs3764261* SNP at the CETP locus to modify lipid metabolism in MetS patients. Plasma lipid concentrations and *rs3764261* genotypes were determined in 424 MetS subjects participating in the CORDIOPREV clinical trial (NCT00924937). Gene-diet interactions were analyzed after a year of dietary intervention (Mediterranean diet (35% fat, 22% MUFA) vs Low-fat diet (28% fat, 12% MUFA)). We found significant gene–diet interactions between *rs3764261* SNP and the dietary pattern for HDL-C ($P = 0.006$) and triglyceride concentrations ($P = 0.040$). Specifically, after 12 months of Mediterranean diet intervention, subjects who were carriers of the minor T allele (TT + TG) displayed higher plasma HDL-C concentrations ($P = 0.021$) and lower triglycerides ($P = 0.020$) compared with those who were homozygous for the major allele (GG). In contrast, in the Low-fat intervention group, no significant differences were found between CETP genotypes after 12 months of dietary treatment. Our data support the notion that the consumption of a Mediterranean diet may play a contributing role in triggering lipid metabolism by interacting with the *rs3764261* SNP at CETP gene locus in MetS patients. Due to the complex nature of gene–environment interactions, dietary adjustment in MetS patients may require a personalized approach.

1. Introduction

Cardiovascular diseases (CVD) continue to be the major causes of morbidity and mortality in modern societies. According to an estimate published by the World Health Organization, 17.3 million people died from CVD in 2008 and by 2030, more than 23 million people will die annually from CVD. Moreover, far from diminishing, cardiometabolic risk factors leading towards the development of CVD, and specifically towards coronary heart disease (CHD), are on the rise. It is important to note that 47% of the reduction in mortality is attributed to treatments of these diseases, while up to 44–50% of reduction has been attributed to changes and control of risk factors, so the current trend is to identify patients at high cardiovascular risk and focus prevention efforts on them [1,2]. In fact, one of every three patients with a previous CHD has a recurrence [3,4]. Therefore, the search for detecting patients at higher

* Corresponding author. Reina Sofia University Hospital, Lipids and Atherosclerosis Research Unit, Avda. Menéndez Pidal, s/n, 14004 Córdoba, Spain. Fax: +34 957218250.
E-mail address: pablopermar@yahoo.es (P. Perez-Martinez).
[1] Antonio Garcia-Rios and Juan Francisco Alcala-Diaz contributed equally to the production of this article.
[2] Pablo Perez-Martinez and Jose Lopez-Miranda contributed equally to this article.

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cardiovascular risk is a priority in most cardiovascular research programs.

In this sense, metabolic syndrome (MetS) is a complex disorder defined by the aggregation of interconnected cardiometabolic risk factors which increases the risk of CVD [5–7]. In fact, MetS has been considered a substantial predictor of CVD and all-cause mortality. However, the etiology of this syndrome is not fully understood and it is known that genetic and environmental factors, including diet, play an important role in its development [8–11]. Moreover, low high-density lipoprotein cholesterol (HDL-C) and increased triglyceride (TG) concentrations are two of the defining factors of MetS and these both lipid parameters are highly influenced by genetic and non-genetic factors.

In this context, cholesteryl ester transfer protein (CETP) gene is a key determinant in lipid metabolism, mainly for HDL-C but also for TG. The protein encoded by this gene is a member of the lipid transfer/lipopolysaccharide binding protein family that transfers cholesteryl esters from HDL to apoB-containing lipoproteins, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) in exchange for TG. A common strategy to examine the CETP function in humans has relied on assessing the clinical phenotype associated with variations in its gene. Genetic variation in the CETP gene has been extensively studied for association with variation in HDL-C in different populations [12–17]. More recently, GWAS studies reported the association of the *rs3764261* SNP with higher HDL-C in Caucasians and this has been confirmed in several large studies including different ethnic groups [18–23]. However, most of this evidence has accumulated from association studies and little is known about whether diet modulates those associations. As we previously mentioned, diet is a major determinant in the development of MetS, given that factors such as HDL-C and TG can be susceptible to lifestyle behavior modification, and for this reason, it is essential to recognize the importance of gene–diet interactions.

Therefore, a clear understanding of how genetic variation in CETP affects HDL-C and its interaction with environmental factors such as diet is still lacking, especially in groups at high risk for CVD such as MetS patients. In an attempt to fill some gaps in our current knowledge, the objective of this work was to explore whether the consumption of a Mediterranean diet enriched in olive oil, compared with a Low-fat diet, interacts with the *rs3764261* CETP SNP to modify lipid metabolism in MetS patients from the CORDIOPREV clinical trial (NCT00924937).

2. Methods

The methodology of the present article is similar to that of recently published articles from the CORDIOPREV cohort [24–26].

2.1. Subjects

The CORDIOPREV study is an ongoing prospective, randomized, single blind, controlled trial including 1002 patients with coronary heart disease (CHD), who had their last coronary event more than six months before enrolment. Thus, the patients were selected with acute coronary syndrome (unstable angina, acute myocardial infarction) and high-risk chronic CHD according to the following criteria:

a) Acute myocardial infarction: The existence of at least 2 of the following 3 signs: angina-type chest pain (or angina equivalents), typical ECG changes (appearance of new Q waves and/or changes in ST segments and/or T waves), and a rise in myocardial enzymes (CPK and/or CPK/MB more than twice the normal laboratory limits). The MB value criterion will prevail in case of discrepancies over the total CPK.
b) Unstable angina: Admission to hospital for angina-type chest pains lasting at least 15 min, both at rest and after exercise, which have increased in frequency and duration in recent days or weeks. The latest episode must have occurred at least 48 h before admission and must be accompanied by at least 1 of the following electrocardiographic or analytical changes:
   - ST depression of at least 0.5 mm in 2 contiguous leads.
   - ST elevation of at least 1 mm in 2 contiguous leads.
   - T-wave inversion of at least 2 mm in 2 contiguous leads.
   - Positive troponin result.
c) Chronic high-risk ischemic heart disease: patients will be included who have been hospitalized for a coronary event and/or stable angina at least once in the past 2 years and who have undergone diagnostic coronary angiography with evidence of severe coronary disease, which is defined as the existence of an epicardia vessel greater than 2.5 mm in diameter with stenosis of >50%.

The objective of the study is to evaluate the efficacy of a Mediterranean diet rich in fat from olive oil, compared with a Low-fat diet, to prevent clinical events and mortality in patients with previous coronary disease in a long-term follow up study. Prevalence of MetS in the CORDIOPREV cohort was 58% [27]. Characteristics of the CORDIOPREV study have been previously released in Clinicaltrials.gov (NCT00924937) and also are summarized in Table 1.

2.2. Study diets

Two potentially healthy diets were used in this study: the Mediterranean diet and the Low-fat diet. The composition was: a) Low-fat diet: 28% fat (12% monounsaturated; 8% polyunsaturated; 8% saturated) and b) Mediterranean diet: 35% fat (22% monounsaturated; 6% polyunsaturated; 7% saturated). To ensure that the main fat source of Mediterranean diet (olive oil) was identical for all patients in this group, the olive oil was provided by the research team. Food packs including low-fat foods (cereals, biscuits, pasta, etc), of similar cost, were provided for the patients randomized to the low-fat group. Dietary assessment and follow-up visits, as well as biochemical measurements have been recently published [26].

Table 1
Baseline characteristics of the patients.

	All patients		Metabolic syndrome		Non-metabolic syndrome		*P*
	Mean	SEM	Mean	SEM	Mean	SEM	
Age (years)	59.5	0.2	60.0	0.3	58.9	0.4	0.189
Male/female	837/165		470/111		367/54		<0.001
Weight (Kg)	85.1	0.4	88.8	0.6	80.1	0.6	<0.001
Waist circumference (cm)	105.1	0.3	108.7	0.4	100.1	0.5	<0.001
BMI (kg/m^2)	31.1	0.1	32.4	0.1	29.3	0.2	<0.001
HDL-C (mg/dL)	42.2	0.3	38.6	0.4	47.1	0.5	<0.001
Glucose (mg/dL)	113.7	1.2	125.9	1.8	97.1	1.0	<0.001
TG (mg/dL)	135.4	2.2	159.9	3.1	102.1	2.2	<0.001
ApoA-1 (mg/dL)	129.6	0.7	124.9	0.8	136.1	1.1	<0.001
TC (mg/dL)	159.0	0.9	158.6	1.3	159.5	1.4	0.255
ApoB (mg/dL)	73.6	0.5	76.1	0.8	70.2	0.8	<0.001
LDL-C (mg/dL)	88.5	0.8	86.3	1.1	91.5	1.2	<0.001

SEM: standard error. Continuous variables were compared using the analysis of variance (ANOVA). Qualitative variables were compared using Chi Square test. BMI = Body mass index; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; TC = total cholesterol; LDL-C = low density lipoprotein; NS = no significant differences ($P > 0.05$).

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