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Effects of lecithin: Cholesterol acyltransferase genotypes, enzyme levels, and activity on high-density lipoprotein levels

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BACKGROUND: Lecithin:cholesterol acyltransferase (LCAT) is one of the key enzymes controlling cholesterol homeostasis and plays a primary role in high-density lipoprotein cholesterol (HDL-C) maturation.

OBJECTIVE: The aim of our study was to evaluate the effects of LCAT gene polymorphisms 511C/T (exon4), 4886C/T (rs5923), and 608C/T (rs5922) on LCAT enzyme level, activity, and HDL-C levels.

METHODS: The study population was selected from consecutive subjects with low (<35 mg/dL) and high HDL-C levels (>65 mg/dL) seen in our lipid clinic. LCAT polymorphisms were analyzed with a restriction fragment length polymorphism assay. LCAT activity and levels were measured by colorimetric enzymatic and enzyme-linked immunoassay methods, respectively.

RESULTS: The 4886C/T polymorphism was the most commonly observed variant of LCAT gene. T-allele frequencies in subjects with low (n = 50) and high (n = 50) HDL-C were 0.54 and 0.37, respectively ($P = .019$). TT genotype was more common among low HDL-C group (30% vs 14%, $P = .05$). The effects of LCAT enzyme appeared to depend on the HDL-C level. In subjects with low HDL-C, LCAT enzyme levels correlated positively with body mass index ($P < .001$, $r = 0.544$), HDL-C ($P = .006$, $r = 0.404$), triglycerides ($P = .001$, $r = 0.487$), total cholesterol ($P < .001$, $r = 0.541$), and low-density lipoprotein-cholesterol ($P = .001$, $r = 0.477$) levels. LCAT activity correlated positively with fasting glucose levels ($P = .008$, $r = 0.390$).

CONCLUSION: LCAT genotype, enzyme level, and activity modulate HDL-C metabolism, particularly among subjects with low HDL-C levels.

High plasma concentrations of high-density lipoprotein cholesterol (HDL-C) are associated with a low risk of atherosclerotic cardiovascular disease. The assessment of HDL-C levels alone for vascular prevention has been challenged, in

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part because of the results of the Investigation of Lipid Level Management to Understand its Impact in Artherosclerotic Events (ILLUMINATE) trial, in which increased HDL-C levels did not reduce the incidence of cardiovascular events.[1] In addition, patients with low HDL associated with Apo A1 Milano have a low indicence of cardiovascular disease.[2] These data illustrate the importance of HDL-C metabolism and not just HDL plasma levels to understand the functionality of HDL.[3] Important differences may exist in HDL-C metabolism among subjects with low versus high HDL-C levels. HDL-C levels are influenced by genetic and environmental factors. Smoking, lack of physical activity, a triglyceride-rich diet, and obesity are among the environmental factors that can reduce HDL-C levels.

Turkish children and adults have lower HDL-C levels compared with other populations.[4–6] Nearly 50% of the Turkish adult population have HDL-C levels below 35 mg/dl.[7,8] Previous investigators report that low HDL-C levels in the Turkish population are likely attributable to genetic factors.[7,8] Different groups examined several genes associated with low HDL-C levels in the Turkish population, including cholesteryl ester transfer protein, ATP binding cassette transporter A1 (ABCA-1), and hepatic lipase (LIPC) gene.[9–11] Five LIPC single nucleotide polymorphisms (SNPs: rs4775041, rs1800588, rs11858164, rs11856322, and rs2242061), cholesteryl ester transfer protein I405V, and *Taq* IB polymorphisms associate with low HDL-C levels among the Turkish population.[9–11]

Lecithin:cholesterol acyltransferase (LCAT) is one of the key enzymes that controls cholesterol homeostasis and transport and has a pivotal role in HDL-C maturation and remodeling.[12] LCAT synthesizes the majority of cholesteryl esters in plasma by transferring a fatty acid from lecithin (phosphatidyl choline) to the 3-hydroxyl group of cholesterol. Although it accentuates reverse cholesterol transport (RCT) from plasma to liver and induces cholesterol degradation, the debate about LCAT's role in RCT and protection against atherosclerosis is ongoing.[13] In the absence of LCAT, RCT can still continue. The main factors that maintain the cholesterol hemostasis within macrophages are pre-β HDL and ABCA1 transporter. Free cholesterol can also be taken up via scavenger receptor class B type I in the liver.[14] Although patients with LCAT deficiency do not show progressive atherosclerosis, a decrease in LCAT activity is associated with an increase in carotid artery intima media thickness.[15] Increased LCAT activity is thought to be atheroprotective, but there are a limited number of studies, and the measurement of LCAT activity is still not standardized.

The number of recent observations and reports about functionality of HDL-C are increasing.[3,16] Therefore, additional data on LCAT's genetic and enzymatic properties should help to understand the role of LCAT in normal HDL-C function. The objective of our study was to evaluate the LCAT gene polymorphisms 511C/T (exon4), 4886C/T (rs5923), and 608C/T (rs5922) and to evaluate the possible relations between the allelic types, LCAT level, and activity on HDL-C levels in subjects with low (<35 mg/dL) or high HDL-C levels (>65 mg/dL).

Methods

Study population

Study population was selected among consecutive patients who applied to general outpatient clinic for lipid testing. Subjects with low and high HDL-C levels were enrolled in the study. Low HDL-C levels were defined according to the National Cholesterol Education Program Adult Treatment Panel guidelines (≤40 mg/dL [≤1.04 mmol/L] in men and ≤50 mg/dL [1.29 ≤mmol/L] in women).[17] High HDL was high HDL-C levels (>65 mg/dL). We enrolled consecutive patients with low and high HDL-C levels (n = 50 in each group) who applied to lipid clinic during a 6-month period in 2007.

In addition to a full history and physical examination, a detailed questionaire was taken from all participants regarding demographic data, lifestyle, dietary habits, smoking, alcohol consumption, family history, and coronary artery disease (CAD). We assessed smoke exposure by asking participants about previous and current history of smoking habits. Smoking history was quantified by number of pack years. Family history of CAD was defined as having a first-degree relative with established CAD before the age of 45 for men, or before menopause for women. CAD was defined as >70% or greater blockage in at least one coronary artery or its major (>2 mm) branches. Exclusion criteria included diabetes mellitus (defined as fasting glucose >126 mg/dL on three different occasions or requirement of treatment for hyperglycemia) and clinical conditions that may cause low HDL-C, including secondary hyperlipidemia (ie, nephrotic syndrome, endocrinologic disease), primary hypertriglyceridemia, thyroid disorders, nephrotic syndrome, liver disease, history of malignancy, treatment with lipid-lowering medications, glucocorticoids, diuretics, and/or β-blockers. Subjects who did not want to participate in the study were excluded.

The subjects were given case numbers and identities were kept confidential. The procedures were in accordance with institutional guidelines. Informed consent was obtained from all subjects, and the study protocol was approved by the institutional review board.

Anthropometric measurements

Weight, height, and blood pressure were measured. The weight of subjects wearing minimal clothing was measured to the nearest 0.1 kg with a portable electronic scale. Each time it was moved, the scale was recalibrated and standardized. Height was measured with a fiberglass tape. Body mass index (BMI) was calculated as weight (kilogram)/height ^{2} (meter). Overweight or obesity were defined by the BMI levels (>25–29.9 and ≥30 kg/m^2, respectively).[17]