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ORIGINAL ARTICLE

Relationship of apolipoprotein E polymorphism with lipid profiles in atherosclerotic coronary artery disease

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Abstract *Aims:* The aim was to determine the relationship between apolipoprotein E (ApoE) gene polymorphisms and lipid profile in patients with coronary artery diseases (CAD), and its role in the prediction of the severity of carotid and coronary atherosclerosis.
Methods and results: One hundred patients were classified by coronary angiography: 80 patients with CAD and 20 controls (normal coronary angiography). Clinical data, carotid sonography, blood lipid profiles and ApoE genotyping (PCR-RFLP) were assessed. CAD patients had significantly increased plasma lipid profiles and carotid intimal-wall thickness (IMT) versus controls. In CAD patients; ApoE genotype frequencies were E3/E3 = 62.50%, E2/E3 = 18.75%, E3/E4 = 17.50%, E2/E4 = 1.25%, E4/E4 = 0 and E2/E2 = 0. But, E3/E4 genotype was significantly higher than controls ($P < 0.05$). Also, in CAD patients; ApoE allele frequencies were E3 = 80.6%, E2 = 10.0% and E4 = 9.4% but, ApoE4 alleles were associated with higher cholesterol ($P = 0.034$) and LDL-c ($P = 0.003$), while ApoE2 alleles were associated with higher triglycerides ($P = 0.037$) versus ApoE3 alleles. However, odds ratio of CAD patients had higher risk with E2/E3 genotypes (2.5-fold), E2 alleles (2.2-fold) and E4 alleles (2.1-fold). Moreover, CAD patients with ApoE4 alleles had significantly higher carotid IMT (1.23 ± 0.26 mm *vs* 0.97 ± 0.2 mm ApoE3, $P = 0.006$; however, non-significant *vs* 1.10 ± 0.40 mm ApoE2 and also, ApoE2 *vs* ApoE3 alleles, $P = 0.633$) and left anterior descending (LAD) coronary artery stenosis (*vs* ApoE3 alleles, $P = 0.016$).
Conclusion: Ischemic patients with carotid and coronary atherosclerosis had significantly higher integration of dyslipidemia and ApoE alleles (ApoE2 with hypertriglyceridemia and ApoE4 with hypercholesterolemia and higher LDL-c). ApoE polymorphism may be an important diagnostic risk biomarker and may implicate therapeutic intervention in atherosclerotic ischemic patients.
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1. Introduction

Coronary artery disease (CAD) is the leading cause of death and premature disability. CAD is a complex disorder resulting from many risk factors. Individuals with genetic predisposition to atherosclerosis have substantial risk of developing CAD, especially at early ages.[1,2] While it is difficult to explore the

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relationship between local vessel wall function and CAD severity, measuring DNA variants such as ApoE polymorphisms may provide a way to assess this link because of its known effect on endothelial cell proliferation.[3] ApoE gene is located at chromosome 19q13.2, and consists of 4 exons and 3 introns spanning 3597 nucleotides, and produces a 299 amino acid polypeptide with a molecular mass of about 34 kDa.[4]

The genetic polymorphism of ApoE results from the existence of 3 common co-dominant alleles (E2, E3, and E4 isoforms) that code for 3 apolipoproteins, resulting in 6 common genotypes (E2E2, E2E3, E2E4, E3E3, E3E4, and E4E4).[5] The most frequent isoform E3 contains a cysteine at residue 112 and an arginine at residue 158, E2 and E4 differ from the E3 isoform in that the E2 isoform contains a cysteine at residue 158 and the E4 contains an arginine at residue 112.[6]

Apolipoprotein E (ApoE) is a plasma glycoprotein and helps lipoprotein clearance from circulation.[7] ApoE is a structural protein of chylomicrons, very-low-density lipoproteins, intermediate-density lipoproteins, and high-density lipoproteins, and serves as a ligand for the uptake of ApoE-containing lipoproteins by the hepatic ApoE receptor or low-density lipoprotein (LDL) receptor.[6] Owing to the complexity of the apoE structure–function, it is not surprising that mutations and polymorphisms of the ApoE gene can have an important impact on protein function. The receptor binding properties of ApoE are strongly influenced by isoform specific amino acid differences as well as the lipidation state of the protein.[7] ApoE3 and ApoE4 bind with similar affinity, while, ApoE2 has just 2% of this binding affinity resulting in dysfunctional lipoprotein metabolism producing atherosclerosis.[8]

ApoE gene polymorphisms are associated with atherosclerosis and play critical roles in lipid metabolism.[3] It may account for 2–16% of the variability of LDL cholesterol levels.[9] Individuals with different ApoE genotypes have different susceptibilities to CAD.[10] Moreover, ApoE is the only one to have shown a convincing association with carotid intima media thickness (IMT).[11] According to meta-analysis study, phenotypes of ApoE and CAD were frequently different with ethnic differences in the studied populations in the world.[3,12] The present study was carried out to determine the relationship of ApoE gene polymorphism with lipid profiles in patients with CAD defined by coronary angiography and its role in the prediction of the severity of carotid and coronary atherosclerosis.

2. Subjects and methods

2.1. Subjects

All the patients were consecutively referred to coronary intensive care unit of the Department of Cardiology in the Menoufiya University Hospital and the Shebin Elkom Teaching Hospital due to an acute myocardial infarction (MI) and who underwent coronary angiography during follow up periods (from Sept. 2009 to June 2011) in this crosssectional study. This study was carried out on 100 CAD patients: 80 CAD patient groups who had coronary artery stenosis in at least one of the major coronary vessels; 20 control patient groups who underwent angiography procedures and had normal coronaries (with acute chest pain other than coronary diseases). Therefore, the age and gender of patients were not matched in both groups.

Full history, general and heart clinical examination, carotid ultrasound and blood samples were done for every patient. Written informed consent was obtained from each participant before inclusion in the study. Ethical approval for this investigation was obtained from the Research Ethics Committee, Faculty of Medicine, Menoufiya University.

The excluding criteria for enrollment into the study included familial hypercholesterolemia, cancer, renal disease, and any other chronic illnesses.

2.2. Carotid ultrasound examination

Carotid artery examination was performed with an ECG-triggered echo-Doppler Acuson 128 XP 10C equipped with a 7.5-MHz linear transducer. Data collected from the right common carotid artery were used for statistical analysis. A preliminary scan verified the presence of plaques and/or stenosis in the carotid tree. Carotid parameters were measured such as carotid intima media thickness (IMT), carotid systolic and diastolic diameters and carotid systolic and diastolic velocities.[11,13,14]

2.3. Determination of CAD severity

According to the results of the coronary angiography, number and percentage of stenosed coronary vessels were classified as previously published.[10] The characteristics of diseased vessels were recorded, including the severity of the most serious stenosis ($\leqslant$75% or $>$75%) and the number of diseased vessels (1, 2, or 3 vessels) including the left main coronary artery (main trunk), circumflex artery (LCA), right coronary artery (RCA) and anterior descending artery (LAD). Also, the coronary artery scoring was performed in order to evaluate the severity of atherosclerosis providing a numerical value for lesions. The severity of CAD was determined using scoring methods[15] as follows severity numbers of normal vessel, coronary lesion with $<$50%, 50–75%, 76–89%, 90–99%, 100% luminal stenosis were 0, 10, 15, 20, 25 points, respectively.

2.4. Lipid profiles analysis

Venous blood sample (5 ml) from an overnight fasting patient was taken for the determination of serum total cholesterol (TC), triglycerides (TG) and HDL-C levels. Lipid profiles were measured by the standard enzymatic colorimetric kits (SPINREACT, Spain). The serum LDL-c was calculated by this formula[16] as TG level did not exceed 400 mg/dl: LDL-c = total cholesterol − (TG/5 + HDL-c).

2.5. DNA analysis

Venous blood sample (5 ml) was drained slowly into a vacunated EDTA tube for the isolation of peripheral blood mononuclear cells (PBMCs) using Lymphoflot solution (Bio Test AG, Germany). Briefly, 5 ml of patient blood was added to an equal volume of saline and mixed carefully. This diluted blood sample was carefully layered onto the Lymphoflot solution (Sodium diatrizoate 11.00% and Ficoll 6.35% w/v) so as not to mix the Lymphoflot solution and the diluted blood sample. The mixture was centrifuged at 1500 rpm for 25 min at 20°C. The upper plasma layer was drawn off, leaving the lymphocyte layer undisturbed at the interface. The lymphocyte layer at the interface was transferred to a clean centrifuge tube

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