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APOA1 and *APOB* polymorphisms and apolipoprotein concentrations as biomarkers of risk in acute coronary syndrome: Relationship with lipid-lowering therapy effectiveness☆

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ABSTRACT

Background and objective: Lipid metabolism alterations contribute to acute coronary syndrome (ACS). rs670, rs5070 and rs693 polymorphisms have shown to modify the risk of cardiovascular disease. Apolipoprotein A-I (ApoA-I) plays a major role in reverse cholesterol transport; apolipoprotein B (ApoB) contributes to accumulation of cholesterol in the plaque. The aim of this study was to investigate the association of rs670 and rs5070 polymorphisms of *APOA1* and rs693 polymorphism of *APOB* with ACS and circulating levels of its proteins and find if ApoB/ApoA-I could be implemented as an independent parameter of risk for cardiovascular disease and as a biomarker of lipid-lowering therapy effectiveness in Mexican population.
Methods: Three hundred patients with ACS and 300 control subjects (CS) were included.
Results: Neither genotype nor allele frequencies of rs670, rs5070 and rs693 polymorphisms showed statistical differences between groups. Serum levels of ApoA-I (195 vs. 161.4 mg/dL; $p < .001$) and ApoB (167 vs. 136.9 mg/dL; $p < .001$) were significantly higher in CS compared with ACS; however, there was no genetic association. Unstable angina patients showed the highest ApoA-I levels (males: 176.3 mg/dL; females: 209.1 mg/dL).
Conclusion: The rs670, rs5070 and rs693 polymorphisms are not genetic susceptibility factors for ACS in Mexican population and had no effect on their apolipoprotein concentrations. In our population, ApoA-I, ApoB and HDL-C could be better biomarkers of cardiovascular risk and could indicate if statins doses reduce atherogenic particles properly.

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Polimorfismos de los genes *APOA1* y *APOB* y concentraciones de sus apolipoproteínas como biomarcadores de riesgo en el síndrome coronario agudo: relación con la efectividad del tratamiento hipolipemiante

R E S U M E N

Antecedentes y objetivo: Las alteraciones en el metabolismo de los lípidos contribuyen al síndrome coronario agudo (SCA). Se ha demostrado que los polimorfismos rs670, rs5070 y rs693 modifican el riesgo de enfermedad cardiovascular. La apolipoproteína A-I (ApoA-I) desempeña un papel principal en el transporte inverso del colesterol; la apolipoproteína B (ApoB) contribuye a la acumulación de colesterol en la placa. El objetivo de este estudio fue investigar la asociación entre los polimorfismos rs670 y rs5070 de *APOA1* y el polimorfismo rs693 de *APOB* con SCA y los niveles circulantes de estas proteínas, e investigar si ApoB/ApoA-I podría introducirse como parámetro independiente predictor de riesgo de la enfermedad cardiovascular y como biomarcador del tratamiento de reducción de lípidos en la población mexicana.
Métodos: Se incluyó a 300 pacientes con SCA y 300 sujetos control (SC).
Resultados: Ni las frecuencias genotípicas ni las alélicas de los polimorfismos rs670, rs5070 y rs693 reflejaron diferencias estadísticamente significativas entre los grupos. Los niveles séricos de ApoA-I (195 frente a 161,4 mg/dl; p < 0,001) y ApoB (167 frente a 136,9 mg/dl; p < 0,001) fueron significativamente superiores en los SC en comparación con los SCA; sin embargo, no existió asociación genética. Los pacientes con angina inestable reflejaron los niveles más elevados de ApoA-I (varones: 176,3 mg/dl; mujeres: 209,1 mg/dl).
Conclusión: Los polimorfismos rs670, rs5070 y rs693 no constituyen factores de susceptibilidad genética para SCA en la población de México y no tienen efecto sobre las concentraciones de sus apolipoproteínas. En nuestra población, ApoA-I, ApoB y c-HDL podrían constituir unos mejores biomarcadores del riesgo cardiovascular, y podrían indicar si las dosis de estatinas reducen debidamente las partículas aterogénicas.

Introduction

In 2012, 17.5 million people died from cardiovascular diseases (CVDs) around the world. Among these deaths, 7.4 million were due to coronary heart disease, a representing 12.4% of the global mortality rate.[1] In Mexico, ischemic heart disease is the leading cause of death in the elderly and ranks second in the general population.[2] According to the *Instituto Nacional de Estadística y Geografía (INEGI)*, there were 88,144 deaths (13.4% of deaths in the Mexican population) from ischemic heart disease in 2015.[3]

The time elapsed after an ischemic event such as in Acute Coronary Syndrome (ACS) is critical because patients face a higher risk for recurrent events or even death.[4] More specific measures to estimate the status and vulnerability of atherosclerotic plaques as well as the efficacy of drugs and diet in lowering lipids levels are needed. Furthermore, it is urgent to revise the predictive potential of risk biomarkers commonly used in medical practice.

Diverse studies of genome-wide association (GWA) have identified candidate loci of susceptibility for cardiovascular diseases including apolipoproteins genes.[5] Indeed, it has been found that some polymorphisms in *APOA1* and *APOB* genes modify the risk of cardiovascular events in different populations.[6,7]

It is well known that the Apo B/ApoA-I ratio is the main factor influencing the risk of myocardial infarction. This conclusion was reached by INTERHEART case–control study that calculated the odd ratios for the top 9 risk factors after analyzing almost 30,000 individuals from 52 countries.[8] A related attempt to predict fatal myocardial infarction is the AMORIS prospective study of >175,000 Swedish individuals, although its database did not contain any information about risk factors, the authors found that apoB serum concentration and ApoB/ApoA-I ratio were the strongest predictors of fatal outcome myocardial infarction.[9] Afterwards, Walldius and Jungner took advantage of the usual lower ApoA-I values in men to propose different cut-off values for the ApoB/ApoA-I ratio: <0.9 in women and <0.8 in men. Accordingly, these authors considered that any value greater than the respective cut-off implies a high risk.[10] Later, Lima et al. combined the results of the INTERHEART and AMORIS studies and proposed a more simplified risk calculation.[11]

In this study we evaluated some polymorphisms of *APOA1* and *APOB* genes and apolipoprotein concentrations as biomarkers of risk in Acute Coronary Syndrome and their relationship with lipid-lowering therapy effectiveness. Furthermore, we analyzed the Apo B/ApoA-I ratio as a possible independent predictor of ischemic events in adults with and without ACS from Western Mexico and compared such ratio with range values proposed by INTERHEART and AMORIS studies.

Materials and methods

Study design and participants

We studied 600 genetically unrelated individuals from Western Mexico. Ethnicity was defined as those having at least two generations of ascendants born in Mexico. These subjects had the following characteristics:

(1) Three hundred patients older than 45 years with ACS, diagnosed according to the American College of Cardiology (ACC) criteria.[12] Result of diagnosis, Biomarkers and routine biochemical test measures were obtained. Samples were collected during the first 24 h after admission to satisfy diagnosis with more specificity.[13] Classical risk factors, as defined by ACC, were categorized as present or absent.
(2) Three hundred Control subjects (CS) older than 45 years. They responded to a questionnaire on their medical history and lifestyle characteristics with absence of previous cardiovascular diseases as the main exclusion criteria. They denied active infections or receiving any treatment.

All subjects were recruited at "Hospital de Especialidades del Centro Médico Nacional de Occidente del Instituto Mexicano del Seguro Social (CMNO-IMSS)." Subjects with overlapping heart disorders or other diseases such as familial hypercholesterolemia, as well as genetically related individuals were excluded.