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Role of heat shock proteins in the cardioprotection of regular moderate alcohol consumption☆

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ABSTRACT

Background and objectives: To study whether the cardioprotective effect of regular alcohol consumption can be explained by the heat shock proteins (HSP), given their pathogenic role in atherosclerosis.
Material and methods: Cross-sectional epidemiological study on 452 men and women aged 40–60. Clinical history, epidemiological survey (frequency of average alcohol consumption) and biochemical analysis was performed; Task Force Chart was applied for classification according to the risk of vascular disease. Intracellular HSPA1A, circulating HSPA1A and HSPD1, and anti-Hsp70/anti-Hsp60 antibodies were quantified by ELISA.
Results: Two hundred and thirty-eight (52.7%) were abstemious or drank <20 g/d of alcohol; 123 (27.2%) drank 20–40 g/d, 66 (14.6%) 40–60 g/d and 25 >60 g/d (5.5%). Two hundred and thirty-nine had no vascular risk (VR) factor or a risk <5%, 161 had moderate VR (10–20%) and 52 had established atherosclerotic disease. Drinkers of 40–60 g/d showed the highest concentrations of intracellular HSPA1A, which were not significant in subjects with moderate VR. Extracellular HSPA1A did not differ and HSPD1 was undetectable. Drinkers of 40–60 g/d and moderate VR or atherosclerotic disease presented the lowest concentrations of anti-Hsp70. The highest levels of serum anti-Hsp60 were shown in heavy male drinkers of >60 g/d especially in subjects with moderate VR, and female drinkers of 40–60 g/d.
Conclusions: The cardioprotective effect of 40–60 g/d of alcohol consumption could be due in part, to increased intracellular HSPA1A, a potent anti-inflammatory protein. Excessive intake of alcohol increases antibodies anti-Hsp60, stimulating proinflammatory cytokines. This fact may explain the mortality from cardiovascular disease in heavy drinkers. The clinical application of antibody anti-Hsps quantification has been proposed in patients at risk in order to detect atherosclerotic disease.

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Proteínas de choque térmico en la cardioprotección del consumo moderado regular de alcohol

Palabras clave:
Alcohol
Proteínas de choque térmico
Ateroesclerosis
Factores de riesgo

RESUMEN

Fundamento y objetivos: Estudiar si el efecto cardioprotector del consumo regular de alcohol puede explicarse a través de las *heat shock proteins* (HSP, «proteínas de choque térmico»), dado su papel etiopatogénico en la ateroesclerosis.
Material y métodos: Estudio epidemiológico trasversal en 452 sujetos de 40-60 años de ambos sexos. Se realizó la historia clínica incluyendo frecuencia del consumo medio de alcohol y análisis bioquímicos, y se estatificó el grado de riesgo coronario según la *Task Force*. Se cuantificaron HSPA1A intracelular, HSPA1A y HSPD1 séricas y anti-Hsp70 y anti-Hsp60 por ELISA.
Resultados: Doscientos treinta y ocho (52,7%) sujetos eran abstemios o bebedores de < 20 g/d de alcohol; 123 (27,2%) bebían 20-40 g/d, 66 (14,6%) 40-60 g/d y 25 > 60 g/d (5,5%). Doscientos treinta y nueve carecían de factores de riesgo vascular (RV) o tenían un RV < 5%; 161 tenían RV moderado (10-20%) y 52 presentaban enfermedad ateroesclerótica instaurada. Los bebedores de 40-60 g/d presentaron máximas concentraciones de HSPA1A intracelular, no significativas en RV moderado. HSPA1A sérica no presentó diferencias y HSPD1 fue indetectable. Los bebedores de 40-60 g/d y RV moderado o

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enfermedad ateroesclerótica presentaron las menores concentraciones de anti-Hsp70. Los anti-Hsp60 fueron máximos en varones bebedores de > 60 g/d y en mujeres bebedoras de 40-60 g/d, especialmente en RV moderado.

Conclusiones: El efecto cardioprotector del consumo de 40-60 g/d de alcohol podría deberse, al menos en parte, al incremento de HSPA1A intracelular, potente proteína antiinflamatoria. El consumo excesivo regular de alcohol se asocia a un aumento de anticuerpos anti-Hsp60, estimulantes de citocinas proinflamatorias; ello podría explicar la mortalidad por enfermedad cardiovascular en estos pacientes. Se ha propuesto la aplicación clínica del seguimiento de anticuerpos anti-Hsp en pacientes en riesgo para detectar enfermedad ateroesclerótica.

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Introduction

In recent years, numerous epidemiological studies have shown the beneficial effects of mild and moderate consumption of alcohol, while experimental studies proved that exposure to moderate doses of alcohol can initiate typical cytoprotective mechanisms.[1] A significant part of this work links regular moderate alcohol consumption with a lower incidence of morbidity and mortality in cardiovascular disease; conversely, excessive consumption correlates with a higher prevalence of coronary heart disease. The relationship between regular alcohol consumption and cardiovascular mortality draw a "U"- or "J"-shaped curve, such that teetotallers and heavy drinkers are at greater risk of cardiovascular disease than light or moderate drinkers.[2] While the most widespread hypothesis is that the cardioprotective effect occurs by the direct action of alcohol regardless of the type of alcoholic beverage consumed,[3] there are numerous studies indicating that consumption of alcoholic beverages rich in polyphenols, such as red wine, provides additional cardiovascular protection because of their specific antioxidants, anti-inflammatory and antithrombotic properties.[4,5]

The suggested mechanisms of the cardioprotective effects mentioned above have included, among others: increased HDL cholesterol and paraoxonase 1 antiatherogenic enzyme associated with HDL cholesterol that inhibits oxidation of low density lipoproteins (LDL)[6]; inhibition of platelet aggregation and decrease of concentrations of coagulation factors[7] and anti-inflammatory action.[8] In this regard, in recent years evidence has been growing regarding the protective effects of regular moderate drinking on the cardiovascular system and that it could be, at least in part, mediated by anti-inflammatory and antioxidants mechanisms[2,9]: in fact, a significant decrease of the C-reactive protein, Interleukin 6 (IL-6), IL-1α, tumour necrosis factor α, fibrinogen and leucocyte count in these patients has been evidenced.[2,10]

Atherosclerosis is a chronic disease of an inflammatory and autoimmune nature, and heat shock proteins (HSP), specifically HSPA1A (Hsp70) and HSPD1 (Hsp60) have been associated with the antigens involved in the initiation of the immune response in atherosclerosis.[11,12] Given the role of HSPs in the pathogenesis of atherosclerosis, the aim of this study was to determine the levels of extra- and intra-cellular HSPA1A, HSPD1 serum levels and anti-Hsp60 and anti-Hsp70 antibodies and their relation to alcohol consumption, in a general population stratified by the degree of vascular risk or the presence of an established atherosclerotic disease.

Materials and methods

Population studied

The description of the study population and its design had been previously conducted.[12] Basically it is an observational, cross-sectional, epidemiological study on the incidence of vascular risk factors (VRF). Inclusion criteria were volunteer subjects randomly selected, aged between 40 and 60 years-old, workers at the Hospital General Universitario Gregorio Marañón in Madrid (Spain), and signing an informed consent. The study was approved by the Research Committee and the Ethics Committee of the Clinical Research Centre. All participants underwent a medical history and answered an epidemiological questionnaire regarding age, personal and family medical history, smoking habits (non-smoker, ex-smoker or current smoker), regular intake of alcohol (if so, daily consumption in grams), treatments and presence of atherosclerotic disease. All interviews were conducted by the same researcher. Exclusion criteria were: pregnant or lactating women, having suffered some kind of systemic infection in the past 3 months, presenting current oncological disease or undergoing radio/chemotherapy treatment, suffering from autoimmune diseases, endocrine disorders (except diabetes), liver disease, congestive renal, haematologic disorder or congenital heart disease.

Alcohol consumption

Each subject was asked about their average consumption habits of different types of alcoholic beverages, including wine, beer and liqueurs or spirits (gin, rum, whisky and others). Considering an alcohol content of 5% for beer, 12% for wine and 40% for spirits, alcohol consumption was calculated in grams per day (g/d) and the following categories were defined: (a) non-drinkers or occasional, not daily consumers of less than 20 g/d; (b) light, regular drinkers 20–40 g/d; (c) moderate regular drinkers 40–60 g/d and (d) excessive regular drinkers who consumed over 60 g/d.

Vascular risk assessment and classification of subjects

The absolute risk of developing cardiovascular disease over a period of time generally set at 10 years is estimated based on the presence of previous coronary disease and the joint assessment of present VRF.[13] Calculating vascular risk in asymptomatic individuals is carried out based on the presence of risk factors. There are various tables available for this, one of the most widely used is the coronary risk Task Force banner.[14] The degree of participants' cardiovascular risk was calculated by considering the presence or absence and severity of each of the conventional VRF, also considering gender, age, smoking habits, the presence of obesity, systolic blood pressure and total cholesterol and LDL cholesterol figures. After applying *Task Force*, participants in the study were classified into 3 groups according to their cardiovascular risk range: Group 0 (G0) or subjects without VRF or risk <5%; Group 1 (G1), subjects with moderate vascular risk (10–20%) without clinical atherosclerotic and Group 2 (G2), subjects with clinically established cardiovascular disease.[15]

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