Oxidative stress and antioxidant enzyme values in lymphomonocytes after an oral unsaturated fat load test in familial hypercholesterolemic subjects

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Oxidative stress (OS) has been observed in conditions affecting the cardiovascular system. Familial hypercholesterolemia (FH) is associated with an increased risk of premature coronary heart disease. In the postprandial state, circulating lipids and lipoproteins can modulate OS status. Our aim was to study the response of lymphomonocyte OS status and reactive oxygen species by-products after an oral unsaturated fat load test (OFLT) in those with FH and to compare this response with that obtained in normolipidemic, normoglycemic subjects. We studied 12 patients with FH and 20 healthy controls. In both groups, lymphomonocyte, oxidized/reduced glutathione ratio, and malondialdehyde were determined at baseline and at 2, 4, 6, and 8 hours after an OFLT. Fasting urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine and isoprostane were measured using standard procedures. In both groups, oxidized/reduced glutathione ratio and malondialdehyde significantly decreased in the postprandial state after the OFLT. Both parameters were significantly higher in the FH group at baseline and during all the postprandial points, but the reduction from the baseline levels was significantly higher in the FH group than in the control group. Urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine was significantly increased in the FH group compared with the healthy control group, indicating a higher fasting OS status. We conclude that subjects with FH exhibited OS levels that were higher than in controls before and after an OFLT, but the improvement in the OS status after the unsaturated fat load was significantly higher in subjects with FH. (Translational Research 2013;161:50–56)

Abbreviations: AUC = area under the curve; BMI = body mass index; CHD = coronary heart disease; 8-oxo-dG = 8-oxo-7,8-dihydro-2′-deoxyguanosine; FH = familial hypercholesterolemia; GPX = glutathione peroxidase; GSH = reduced glutathione; GSSG = oxidized glutathione;

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HPLC = high-performance liquid chromatography; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MDA = malondialdehyde; OFLT = oral fat load test; OS = oxidative stress; ROS = reactive oxygen species; VLDL = very low-density lipoprotein

AT A GLANCE COMMENTARY

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Background

Familial hypercholesterolemia (FH) is an autosomal dominant disease characterized by a marked increased risk of premature coronary heart disease. Previous studies have shown that subjects with FH have elevated fasting concentrations of remnant particles and oxidative stress, possibly related with increased cardiovascular risk. However, the knowledge of postprandial oxidative stress is limited.

Translational Significance

The decrease of oxidative stress status in patients with FH after an oral fat load with unsaturated fat could be of great interest because the modification of dietary patterns in this group of subjects could be beneficial to reduce the incidence of coronary heart disease.

Oxidative stress (OS), an excessive production of reactive oxygen species (ROS) overcoming antioxidant defense mechanisms, has been observed in conditions affecting the cardiovascular system, such as smoking, hypercholesterolemia, diabetes, and hypertension.[1–3] OS may lead to many cellular events, such as inactivation of nitric oxidase, oxidative modifications of DNA and proteins, lipid oxidation, enhanced mitogenicity, and apoptosis of vascular cells, that contribute to the development and progression of atherosclerosis.[4] Moreover, OS may be modulated by factors such as age, gender, nutritional status, and nutritional components.

The degradation of ROS is carried out by antioxidant enzymes: glutathione peroxidase (GPX), superoxide dismutase, catalase, and the glutathione system (reduced glutathione [GSH] and oxidized glutathione [GSSG]). An increase in ROS production overwhelming the capacity of antioxidant enzymes leads to the generation of OS.[5–7] These changes may induce alterations in the structure and function of endothelial cells and contribute to the initiation and progression of the atherosclerotic plaque.[4,6–8]

In the postprandial state, circulating lipids and lipoproteins can modulate OS status. Several fat meal tests, dietary interventions, and oral fat load tests (OFLTs) in healthy people have shown that the type of fat can regulate OS status.[7,8] Beneficial effects have been shown when unsaturated fat was used compared with saturated fat.[6,9]

Familial hypercholesterolemia (FH) is an autosomal dominant disease characterized by a marked increase of low-density lipoprotein cholesterol (LDL-C) and associated with an increased risk of premature coronary heart disease (CHD).[10] Our group and others have demonstrated that fasting OS is increased in patients with FH and is particularly pronounced in patients with vascular disease.[11–13] In addition, Dane-Stewart et al[14] demonstrated that patients with FH have elevated fasting plasma concentrations of remnant particles, possibly reflecting an altered postprandial lipemia due to the important role that low-density lipoprotein (LDL) receptor plays in clearing intermediate-density lipoprotein, very low-density lipoprotein (VLDL), and remnant particles in the postprandial state. Other groups have shown that mutations on the LDL receptor gene cause altered LDL receptors in patients with FH, with decreased activity in clearing for cleaning postprandial lipids particles.[15] This alteration could contribute to the development of atherosclerosis in such patients.

The present study was undertaken to analyze the OS status by measuring GSH and GSSG and malondialdehyde (MDA) in lymphomonocytes, key cells in the atherosclerosis process, from patients with FH during an OFLT. We hypothesized that postprandial intervention with unsaturated fat could decrease the fasting OS status in patients with FH. Therefore, we compared the FH postprandial OS status response after an OFLT with unsaturated fat with that obtained in healthy subjects. We are unaware of studies having tested this hypothesis in patients with FH.

SUBJECTS AND METHODS

Subjects. Twelve patients with FH from our outpatient clinic and 20 healthy volunteers ranging in age from 18 to 65 years were randomly recruited. All subjects were Caucasian, lived in the Valencia region, and gave written informed consent to participate in the research protocol approved by our institution Hospital Clinico Universitario de Valencia. The research protocol conformed to the ethical guidelines for human and animal research and was approved by the ethics committee of our centre.

Diagnostic criteria for FH included plasma levels of total and LDL-C above the 95th percentile corrected