Lipid profile and inflammatory markers associated with estrogen receptor α PvuII and *XbaI* gene polymorphisms

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Estrogen is established to influence lipoprotein metabolism and inflammatory markers. Alternations in estrogen receptor α (ESR1) expression and function may affect the role of estrogen in this regard. The aim of this study was to determine whether ESR1 PvuII and XbaI gene polymorphisms have effects on lipoprotein (a) as well as inflammatory variables in an Iranian population. Three hundred and ninety seven consecutive participants (228 men, 57.4%) who were admitted at our center for elective coronary angiography because of symptoms related to coronary artery disease (CAD) were enrolled in our study. Total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride levels were determined by standard methods using commercial kits. Low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula. The lipoprotein (a) levels were measured by ELISA method using Biopool kit, and the CRP concentrations were determined by Latex Immunoturbidometry. The presence of PvuII and XbaI polymorphisms within the ESR gene were analyzed using polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP). The frequency of homozygous and heterozygous were 25.9% and 50.1%, for PvuII genotypes, and the frequency was 23.7% and 48.6%, for XbaI genotypes, respectively. After adjusting for CAD and age, no impacts of ESR1 PvuII and XbaI polymorphisms were found on lipid profile, lipoprotein (a) level, and quantitative CRP either in total population or in subgroups stratified by gender. In conclusion, our data demonstrate that ESR1 PvuII and XbaI gene polymorphisms did not seem to have an effect on lipoprotein metabolism or on inflammatory variables such as CRP. (Translational Research 2009;153:288–295)

Abbreviations: CAD = coronary artery disease; CRP = C-reactive protein; ESR1 = estrogen receptor α; HDL = high-density lipoprotein; HRT = hormone replacement therapy; Lp(a) = lipoprotein (a); LDL = low-density lipoprotein; PCR-RFLP = polymerase chain reaction–based restriction fragment length polymorphism; SD = standard deviation; SNPs = single nucleotide polymorphisms

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AT A GLANCE COMMENTARY

Background

The cardioprotective effects of estrogen have been attributed in part to its effects on serum lipid profile and lipoprotein metabolism. The effects of estrogens on the vascular system are mediated mainly through estrogen receptor α (ESR1); however, the previous results about the association between ESR1 PvuII and XbaI gene polymorphisms with lipid profile and inflammatory markers are controversial.

Translational Significance

Determination of the aforementioned association will be beneficial to identify the genetic susceptibility for higher levels of lipids and inflammatory markers and consequently for cardiovascular disease. It may also shed light on decision making for using hormone therapy in postmenopausal women.

Estrogen seems to be a natural vasoprotective agent. Although the direct effects of estrogen on vascular tissue may contribute markedly to the physiologic effects of this hormone, the cardioprotective effects of estrogen have been attributed in part to its effects on serum lipid profile and lipoprotein metabolism.[1] Estrogen increases serum high-density lipoprotein (HDL) cholesterol and triglyceride concentrations and decreases serum low-density lipoprotein (LDL) cholesterol and lipoprotein (a) [Lp(a)] concentrations principally by affecting the hepatic expression of genes involved in lipoprotein metabolism.[2,3] Despite these beneficial effects, recent clinical trials have failed to show that hormone replacement therapy (HRT) is associated with a lower rate of coronary artery disease (CAD) in postmenopausal women, and some trials have suggested an increased risk of CAD during the 1st year after randomization.[4-6] Thus, estrogen might also have detrimental impacts on the cardiovascular system; for example, it may exert a proinflammatory action. Some studies have revealed an increase in C-reactive protein (CRP) levels during oral HRT in postmenopausal women.[7-9]

The effects of estrogens on the vascular system are mediated mainly through estrogen receptor α (ESR1), which is a member of the nuclear hormone receptor superfamily and acts as a ligand-activated transcription factor.[10] The human ESR1 is located on the long arm of chromosome 6. It has 6 domains encoded by 8 exons separated by 7 intronic regions. A variety of polymorphisms of the ESR1 gene—both single-nucleotide polymorphisms (SNPs) and tandem repeats—has been investigated in candidate gene association studies, and associations between many polymorphisms in ESR1 with several pathologic conditions, which include cardiovascular disorders,[11-13] were observed. Of the polymorphisms identified in the ESR1 gene, 2 SNPs (PvuII and XbaI) are most widely investigated. The PvuII polymorphism (also known as the c.454-397T>C, IVS1-397 T/C, and rs2234693) and the XbaI polymorphism (also known as the c.454-351A>G, IVS1-351 A/G, and rs9340799) are located in the 1st intron of ESR1 gene, 397 and 351 base pairs upstream of exon 2, respectively.

The aim of this study was to determine whether estrogen receptor α (ESR1) PvuII and XbaI gene polymorphisms have effects on lipid profile as well as inflammatory variables in an Iranian population.

METHODS

Three hundred and ninety seven consecutive participants (228 men, 57.4%) who were admitted at our center for elective coronary angiography for symptoms related to CAD were enrolled in our study. The research was conducted according to the Declaration of Helsinki. The study protocol was approved by the local ethical committee. Written informed consent was obtained from all patients, who approved the collection of blood samples for scientific research.

Analyzed variables included age, male sex, cigarette smoking, diabetes, hypercholesterolemia, and hypertension. Patients who currently smoked any sort of tobacco or who had quit smoking for less than 1 month were considered smokers. Hyperlipidemia was defined as plasma total cholesterol level of 200 mg/dL or higher, LDL-cholesterol level 130 mg/dL or higher, or being on lipid-lowering drugs at the time of study. Patients were considered to have hypertension if they had received such a diagnosis with arterial pressure more than 140/90 mm Hg or were being treated with antihypertensive medications. Patients were considered to have diabetes providing that they were taking insulin, oral hypoglycemic agents, had previously received such treatments, or were currently following a regulated diet to control the condition. Patients with a lack of awareness of their history of diabetes were defined as those who meet the new World Health Organization criteria for diagnosing diabetes mellitus.

Coronary angiography was performed from the percutaneous femoral approach using standard angiographic techniques. The presence and severity of CAD was determined by Gensini score, which has been described previously.[14] Briefly, the coronary arterial tree was divided into segments with multiplying factors according