Influence of genetic polymorphisms of glutathione S-transferases T1 and M1 on serum lipid parameters

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ABSTRACT

Objectives: To determine the effect of genetic polymorphisms of glutathione S-transferase theta 1 (GSTT1) and GSTM1 on serum levels of lipid parameters.

Methods: We conducted this cross-sectional study on 152 adult healthy subjects (54 females and 98 males) from June 2004 to September 2004. The participants in our study were recruited from the Research Clinic in Abarku (Yazd province, central part of Iran). There were unrelated Iranian Muslims. The genotypes of GSTT1 and GSTM1 were determined using a polymerase chain reaction based method. After an overnight fasting, serum lipid indices including triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured.

Results: There were significant partial correlation coefficients between levels of TG (r= -0.4833, df=48, p<0.001) and TG/HDL-C ratio (r= -0.4041, df=48, p=0.004) and numbers of active GST genotypes in females after controlling for age and body mass index (BMI). In males, the level of TG increased as a function of numbers of active GST genotypes after controlling for age and BMI (r= +0.2082, df=94, p=0.042). There were significant differences between females and males.

Conclusions: Data show that genetic polymorphisms of GSTM1 and GSTT1 modulate levels of TG, and TG/HDL-C in females.

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Coronary heart disease (CHD) is a multifactorial disease caused by the interaction of several genes and environmental factors. The CHD risk factors, including hypercholesterolemia, hyperlipidemia, age, hypertension, diabetes mellitus, and smoking are associated with enhanced oxidative stress.[1] In vivo oxidation products, namely free radicals, and reactive oxygen species (ROS), have been associated with the etiology or progression of several diseases and aging.[2] Oxidation and antioxidant balance in the body are a crucial factor in the pathophysiology of various diseases. Oxidative stress, an imbalance between oxidant production and antioxidant defenses in favor of the former has been shown to be involved in the atherogenesis process, aging, cancer, neurodegenerative and cardiovascular diseases.[2,3] Glutathione S-transferase (GST) system consists of a large multigenic group of detoxifying enzymes whose activity, catalyzing the conjugation of toxic and mutagenic compounds with glutathione, is essential for cell protection. Both GSTM1 and GSTT1 are known to be polymorphic in human and both of them have null alleles resulting from gene deletion. The functional consequences of the GSTM1 and GSTT1 null genotypes are obvious in terms of enzyme activity: no gene, no enzyme, and no activity.[4] Genetic polymorphisms in GSTM1 and GSTT1 have been defined, and disease-association studies were conducted for various diseases. The protective effect of the GSTM1 and GSTT1 null genotypes against CHD is reported.[5,6] However, other studies found no association.[7,8] We showed the influence of GSTM1 and GSTT1 polymorphisms on the systolic and diastolic blood pressure in normotensive healthy subjects[9] and persons environmentally exposed to natural gas containing H_2S.[10] Also genetic polymorphisms of GSTM1 and GSTT1 are associated with several types of cancers.[11-14] Several epidemiological studies indicated that cancers and cardiovascular disease have common risk factors, including oxidative stress. The metabolizing enzymes of GSTs are involved in modulation of oxidative stress. The present study was carried out to explore the role of genetic polymorphisms of enzymes involved in modulation of oxidative stress on serum lipid parameters.

Methods. This cross-sectional study was conducted on 152 adult healthy subjects (54 females and 98 males) from June 2004 to September 2004. The participants in

our study were recruited from the Research Clinic in Abarku (Yazd province, central part of Iran). There were unrelated Iranian Muslims. An informed consent was obtained from all participants. This study was approved by the Institutional Review Board by the Markaz, Behdasht, Abarku, Iran. At the time of blood donation, participants completed a brief questioner that ascertained smoking status, age, and alcohol consumption, history of cancer, diabetes, and hypertension. The subjects had a negative history of alcohol consumption. Participants with diabetes, asthma, history of cancer, and a self-reported history of hypertension that was corroborated by the family physician, or had coexisting illnesses were excluded from the study. Patients with asthma and cancer were excluded due to the association of polymorphisms on GSTM1 and GSTT1.[11-16] After an overnight fasting, blood samples were collected into heparin-containing tubes. Serum lipid indices including triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured. Low density lipoprotein cholesterol (LDL-C) concentrations were calculated according to the Friedewald formula.[17] The polymerase chain reaction (PCR) conditions for determining GSTM1 and GSTT1 genotypes, evaluating the polymorphisms and laboratory quality control were the same as that reported previously.[11]

Statistical analyses were expressed as mean±SD. After controlling for age and body mass index (BMI), the partial correlation coefficients between the lipid parameters and numbers of active GST genotypes were determined. The analyses were carried out separately for males and females. Data analysis was performed using SPSS software version 11.5. A probability of $p<0.05$ was considered statistically significant difference.

Results. It has already been shown that GSTM1 and GSTT1 are involved in detoxification of a variety of compounds some of which overlap between these enzymes and some of which are highly specific.[18] To investigate whether one null GST genotype could be compensated by an active genotype for the other isoenzymes, the mean values of studied parameters were compared with each others in accordance with the zero, one, and 2 active-genotypes of GSTs in females and males (**Table 1**). There were significant partial correlation coefficients between levels of TG (r= -0.4833, df=48, $p<0.001$) and TG/HDL-C ratio (r= -0.4041, df=48, $p=0.004$) and the number of active GST genotypes in females after controlling for age and BMI. This means that females with no active GST gene (double null genotype for GSTT1 and GSTM1), showed higher levels of TG and TG/HDL-C ratio in comparison with females with at least one active genes. In males, the level of TG increased as a function of number of active GST genotypes after controlling for age and BMI. This correlation was significant at borderline (r= +0.2082, df=94, $p=0.042$). There were significant differences between females and males.

Table 1 - Mean values ± SD of serum lipid parameters, age and BMI in females and males according to their number of active genotypes of GSTM1 and GSTT1 and partial correlations between lipid parameters and numbers of active GSTs genotypes after controlling for age and BMI.

Parameters	Numbers of active genotypes			Partial Correlations*		
	0	1	2	r	df	*P*-value
Females†						
Total cholesterol (mg/dl)	232.8 ± 47.8	189.3 ± 36.7	186.9 ± 34.8	-0.1255	48	0.385
Triglyceride (mg/dl)	244.0 ± 81.1	155.2 ± 42.8	133.5 ± 32.5	-0.4833	48	<0.001
HDL-C (mg/dl)	43.5 ± 6.9	41.9 ± 9.5	45.9 ± 11.2	+0.1486	48	0.303
LDL-C (mg/dl)	140.5 ± 46.0	115.7 ± 38.9	113.1 ± 34.0	-0.0567	48	0.696
TG/HDL-C ratio	5.91 ± 2.6	3.95 ± 1.61	3.14 ± 1.35	-0.4041	48	0.004
Age (years)	40.0 ± 28.2	38.7 ± 12.6	33.7 ± 9.1	-	-	-
BMI (Kg/m^2)	28.2 ± 1.0	26.3 ± 4.3	25.7 ± 3.9	-	-	-
Males‡						
TC (mg/dl)	209.2 ± 45.3	192.5 ± 36.2	197.4 ± 38.8	+0.0835	94	0.421
TG (mg/dl)	170.3 ± 45.1	163.8 ± 51.2	198.4 ± 82.3	+0.2082	94	0.042
HDL-C (mg/dl)	39.2 ± 10.2	39.6 ± 11.9	39.1 ± 10.5	-0.0274	94	0.791
LDL-C (mg/dl)	135.8 ± 45.6	120.4 ± 33.9	118.1 ± 38.1	-0.1624	94	0.114
TG/HDL-C ratio	4.76 ± 2.14	4.47 ±1.86	5.55 ± 3.43	+0.1698	94	0.098
Age (years)	36.9 ± 8.3	35.9 ± 8.3	40.1 ± 10.4	-	-	-
BMI (Kg/m^2)	26.8 ± 3.5	25.0 ± 3.8	25.8 ± 3.8	-	-	-

*After controlling for age and BMI, †Number of subjects with 0, 1, and 2 of the active genotypes were equal to 4, 27, and 23, ‡Number of subjects with 0, 1, and 2 of the active genotypes were equal to 16, 40, and 42, HDL-C - high density lipoprotein cholesterol, LDL-C - low density lipoprotein cholesterol, BMI - body mass index, GST - glutathione S-transferase

Discussion. The gender specific associations between genetic polymorphisms and serum TG values were reported previously.[19-21] It was reported that the effects of the fatty acid-binding protein 2 (FABP2) genetic polymorphism on TG, LDL-C and BMI were associated with gender differences among non-diabetic Japanese-American subjects.[19] The microsomal triglyceride transfer protein (MTP)-493 GT polymorphism modulates plasma TG values of familial hypercholesterolemia subjects pre- and post- treatment with atorvastatin in a gender-specific way.[20] The present findings also indicated that genetic polymorphisms of GSTT1 and GSTM1 influence serum values of some lipid indices in a gender specific way. Gender-related differences in the expression of GST isoenzymes may be the cause of the present results. Such differences have been found in human skin,[22] and antrum.[23] The null genotype of GSTM1 is associated with senile cataract susceptibility in females but not in males.[24] On the other hand, exposure to different environmental or occupational oxidant agents, for males and females, would be taking into accounts. These results imply that further studies of the precise mechanisms by which the GSTs genetic polymorphism influences the serum lipid parameters and natural history of cardiovascular disease is merited.

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