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Original article:

GENETIC POLYMORPHISMS OF GLUTATHIONE S-TRANSFERASE M1 (*GSTM1*) AND T1 (*GSTT1*) AND SUSCEPTIBILITY TO PRE-ECLAMPSIA: A CASE-CONTROL STUDY AND A META-ANALYSIS

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ABSTRACT

The objective of the present hospital-based case-control study was to assess the association between glutathione S-transferase M1 (*GSTM1*) and T1 (*GSTT1*) genetic polymorphisms and susceptibility to pre-eclampsia (PE) in Shiraz (Fars province, southern Iran). A total of 200 healthy pregnant women and 151 pre-eclamptic women were included. The healthy control group was frequency matched with the age of the pre-eclamptic women. Control women had neither PE in current pregnancy nor history of pregnancies with PE previously. The genotypes of *GSTT1* and *GSTM1* polymorphisms were determined using a PCR-based method. Neither *GSTM1* null genotype (OR=1.07, 95 % CI: 0.70-1.64, P=0.736) nor *GSTT1* null genotype (OR=0.73, 95 % CI: 0.44-1.21, P=0.233) was associated with risk of PE. Association between combination genotypes and risk of PE was not significant. When family history was entered as a covariate in analysis, adjusted ORs revealed that neither *GSTM1* nor *GSTT1* polymorphisms was associated with risk of PE. For meta-analysis, we identified 5 eligible studies, including 1217 subjects (515 patients, and 702 healthy controls) in relation to the study polymorphisms and risk of PE. Our present meta-analysis indicated that there neither *GSTM1* (OR=0.99, 95 % CI: 0.78-1.25, P=0.955) nor *GSTT1* polymorphisms (OR=0.85, 95 % CI: 0.66-1.10, P=0.223) was associated with susceptibility to PE. Taken together it seems that the polymorphisms of *GSTM1* and *GSTT1* are not risk factors for PE. Further investigations adjusting for confounding factors are needed to confirm the present findings.

Keywords: *GSTM1*, *GSTT1,* meta–analysis, polymorphism, pre-eclampsia

INTRODUCTION

Pre-eclampsia (PE) is a major obstetric problem leading to substantial maternal and perinatal morbidity and mortality worldwide, especially in developing countries. Clinically PE presents as a maternal syndrome, including hypertension and proteinuria after second half of pregnancy. Based on family and twin studies pre-eclampsia was found to have a genetic component (Robert and Cooper, 2001; Sibai et al., 2005). Consanguinity in terms of first cousin once removed increased the risk of PE, in comparison with unrelated marriages (Anvar et al., 2010). Genome-wide searches have identified several chromosomal bands associated with PE (Chappell and Morgan, 2006; Mütze et al., 2008).

Oxidative stress is known to take part of normal pregnant physiologic process. The pathophysiology of PE is known to be associated with unbalanced between oxidative stress due to the production of reactive oxygen species and the ability of antioxidant process (Dekker and Sibai, 1998; Chamy et al., 2006). Glutathione S-transferases (GSTs) (EC: 2.5.1.18) are major phase II enzymes involved in the detoxi-

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fication and are known as oxidative stress related genes (Hayes et al., 2005). Currently several classes of *GSTs* are known in human including mu and theta. Genetic polymorphisms in genes encoding *GSTM1* (a member of class mu; MIM: 138350), and *GSTT1* (a member of class theta; MIM: 600436) have been defined. The *GSTM1-0* and *GSTT1-0* alleles represent deletions of *GSTM1* and *GSTT1* genes, respectively and result in a loss of enzymatic activity (Harada et al., 1992; Pemble et al., 1994).

Several studies have suggested that women who develop PE are at increased risk of cardiovascular complications later in life (Ramsay et al., 2003; Haukkamaa et al., 2004). Epidemiological studies indicated that cancers, cardiovascular disease, and PE have common risk factors, including oxidative stress (Squier 2001; Moskovitz et al., 2002; Ramsay et al., 2003; Haukkamaa et al., 2004; Sibai et al., 2005). The *GSTM1* and *GSTT1* null genotypes have been linked with an increased risk of several multifactorial traits including cancers and cardiovascular diseases (Harada et al., 1992; Wilson et al., 2000; Saadat et al., 2004a, b; Saadat and Farvardine-Jahromi, 2006; Saadat, 2006, 2007; Unal et al., 2007; Wang et al., 2008; Tang et al., 2010).

Taken together, it is speculated that polymorphisms of *GSTT1* and *GSTM1* may be associated with risk of PE. Previously several studies have been conducted to assess the role of *GSTM1* and *GSTT1* in PE. They found no relation between these polymorphisms and risk of PE (Zusterzeel et al., 2000; Cetin et al., 2005; Kim et al., 2005; Zhang et al., 2008). Zusterzeel et al., (2000) found that the null genotype of *GSTT1* significantly decreased the risk of PE. Therefore the association between *GSTT1* and susceptibility to PE is an open question. However, there is no data on association between susceptibility to PE and combination genotypes of *GSTT1* and *GSTM1*. Therefore the present case-control study and meta-analysis were done.

MATERIALS AND METHODS

Case-control study

In the present hospital-based case-control study participants were recruited from the delivery ward at Zainabeieh and Hafez Hospitals, Shiraz University of Medical Sciences, between January 2009 and January 2010. Pre-eclamptic cases (n=151) were defined as persistent blood pressure above 140/90 mmHg and proteinuria of more than 0.3g/24h, developing after 20 weeks of pregnancy (mean age $\pm$ SD, 28.1 $\pm$ 5.4 years).

Exclusion criteria were as follows: altered renal function, chronic hypertension, hypercholesterolemia, cardiovascular diseases, diabetes, asthma, cancers, cataract, psychiatric disorders such as schizophrenia and bipolar disease, twin pregnancies, recurrent miscarriages, fetal growth retardation, and abrutio placenta.

A total of 200 healthy pregnant women frequency matched with the patients according to age were also studied, as a control group (mean age $\pm$ SD, 27.2 $\pm$ 5.0 years). Control women had neither PE in current pregnancy nor history of pregnancies with PE previously. This study was approved by the institutional review board of local ethics committee at our department in Shiraz University. Informed consent was obtained from all participants.

Because Iranian population is one of the most heterogeneous populations (Amirshahi et al., 1989; Walter et al., 1991; Mohamadynejad and Saadat, 2008; Rafiee et al., 2010) we selected our patients and controls from the same ethnical religious group (Persian Muslims living in Fars province, southern Iran). At the time of blood donation, a brief questionnaire that ascertained age, history of cancers, cataract, and asthma was completed. We excluded patients and control subjects with cataract or past history of cataract surgery, asthma, past history of malignancy (treated or on treatment), cardiovascular disease that on medication and known cases of glaucoma, because these traits were associated with *GSTM1* and/or *GSTT1* polymorphisms (Harada et al.,

1992; Wilson et al., 2000; Saadat et al., 2004a, b; Saadat and Farvardine-Jahromi, 2006; Saadat, 2006, 2007; Unal et al., 2007; Wang et al., 2008; Tang et al., 2010).

A woman with at least one first-degree relative with PE or own history of PE is considered to have a positive family history.

Extraction of DNA and genotyping analysis

At the time of delivery, blood samples were obtained from participants and stored immediately at -80 °C. Genomic DNA was isolated from whole blood. The PCR conditions for determining *GSTT1* and *GSTM1* genotypes were the same as reported previously. The absence of amplified product was consistent with the null genotypes of *GSTT1* and *GSTM1*. Successful amplification by β-globin specific primers confirmed the proper function of the PCR reaction. Evaluating the polymorphism and laboratory quality control were the same as that reported previously (Rafiee et al., 2010).

To ensure laboratory quality control, two independent readers interpreted the gel photographs. Any sample with ambiguous results was re-tested, and a random selection of 15 % of all samples was repeated, no discrepancy was discovered upon replicate testing (Rafiee et al., 2010).

Statistical analysis

The association between genetic polymorphisms and the risk of PE was examined by use of the odds ratios (OR) and 95 % of confidence intervals (CIs). Because there was significant difference between patients and controls for family history for PE, the ORs were adjusted for family history for PE.

To investigate whether one null genotype could be compensated by an active genotype for the other isoenzymes, we considered the association between combinations of the genotypes and risk of PE. The reference group consisted of individuals who had two active genotypes. Also χ^2 for linear trend for presence of 0, 1, and 2 null genotypes and risk of PE was calculated.

Statistical analysis was performed using SPSS statistical software package (version 11.5) for windows (SPSS Inc., Chicago, IL, USA). A probability of $p < 0.05$ was considered statistically significant. All P values were two-tailed.

Identification of studies for meta-analysis

Eligible studies were identified by searching the database of Medline database (US National Library of Medicine, Bethesda, Maryland), PubMed (National Center for Biotechnology, National Library of Medicine), ISI Web of Knowledge, Elsevier ScienceDirect, EMBASE, EBSCOhost Research Databases, Scopus, DOAJ (Directory of Open Access Journals), ProQuest, CAB Abstract, and SID (Scientific Information Database) for relevant reports published before April 2011 using the following search terms: "*GSTT1*", "*GSTM1*" "polymorphism", and "preeclampsia". Furthermore, references cited in the retrieved articles were screened to trace additional relevant studies.

The full texts of the candidate articles were examined to determine whether they contained sufficient information on the association of simultaneously *GSTT1* and *GSTM1* polymorphisms and the risk of PE. Articles were included in the meta-analysis if they met all the following criteria: (1) unrelated case-control experimental design, (2) genotypic frequency documentation, (3) article published in English. Review articles, case-only articles, repeated literatures, and abstracts were excluded. All together, 4 articles published in English met the inclusion criteria (Zusterzeel et al., 2000; Cetin et al., 2005; Kim et al., 2005; Zhang et al., 2008). The application of these criteria yielded 5 case-control studies eligible for meta-analysis. In all of the studies, the polymorphism was determined by PCR assays.

All studies were reviewed twice and extracted the data using a standardized form. Data were collected on the authors, year of publication, country of origin, ethnicity and numbers of genotypes of *GSTT1* and *GSTM1* among cases and controls.

Statistical analysis

The presence of between-study heterogeneity was investigated using the chi-square-based Cochran's Q statistic test (DerSimonian and Laird, 1986). The association was measured using random-effect or fixed-effect models according to the studies' heterogeneity. The fixed-effects method assumes no significant heterogeneity between the results of the individual studies being pooled, whereas, the random-effects method allows for such heterogeneity. The fixed-effects and random-effects methods were used by Mantel-Haenszel (1959) and DerSimonian and Laird methods (1986), respectively. Possible causes of heterogeneity were investigated by subgroup analyses based on geographic location and ethnicity.

RESULTS

Case-control study

Selective risk factors for PE were compared between case and control groups (Table 1). Family history of PE was significantly associated with elevated of PE risk (OR=24.5, 95 % CI: 7.41-81.2, P < 0.001). There was no significant association between smoking status and PE (OR=0.37, 95 % CI: 0.07-1.80, P=0.370).

The prevalence of *GSTM1* and *GSTT1* null genotypes were 50.5 and 26.0 percent, respectively, in control subjects. Among patients, the frequency of null genotypes of *GSTM1* and *GSTT1* were 52.3 and 20.5 percent, respectively. Table 2 shows the association between the genetic polymorphisms and PE risk. Neither *GSTM1* null genotype (OR=1.07, 95 % CI: 0.70-1.64, P=0.736) nor *GSTT1* null genotype (OR=0.73, 95 % CI: 0.44-1.21, P=0.233) were associated with risk of PE.

Considering that there was significant difference for family history for PE between cases and controls, the family history for PE of participants was used as a covariate in further analysis. When family history was entered as a covariate in multivariate analysis, adjusted ORs revealed that neither *GSTM1* (OR=1.16., 95 % CI: 0.73-1.85, P=0.512) nor *GSTT1* polymorphisms (OR=0.76, 95 % CI: 0.44-1.32, P=0.338) were associated with risk of PE (Table 2).

In order to investigate whether one null genotype could be compensated by an active genotype for the other isoenzymes, in further analysis we study the association between genotypic combination and risk of PE. There was no association between combination genotypes and risk of PE before and after adjustment for family history for PE (Table 2). There was no linear trend for presence of 0, 1, and 2 null genotypes and risk of PE (χ^2=0.251, P=0.616).

Table 1: Comparisons of selective risk factors between pre-eclamptic patients and control subjects

Characteristic	Control	Case	OR	95 % CI	P-value
Family history of PE					
No	197	107	1.0		
Yes	3	40	24.5	7.41-81.2	<0.001
Missing	0	4			
Parity					
Nulliparity	95	78	1.0		
Other parities	105	73	0.85	0.55-1.29	0.441
Smoking habit					
No	193	149	1.0		
Yes	7	2	0.37	0.07-1.80	0.370

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Table 2: Association between polymorphisms of *GSTM1* and *GSTT1* and risk of pre-eclampsia

Genotypes		Control	Case	OR*	95% CI	P-value	OR**	95% CI	P-value
***GSTM1* polymorphism**									
Active		99	72	1.0			1.0		
Null		101	79	1.07	0.70-1.64	0.736	1.16	0.73-1.85	0.512
***GSTT1* polymorphism**									
Active		148	120	1.0			1.0		
Null		52	31	0.73	0.44-1.32	0.233	0.76	0.44-1.32	0.338
Combination of genotypes									
GSTM1	***GSTT1***								
Active	**Active**	76	59	1.0			1.0		
Null	**Active**	72	61	1.09	0.67-1.76	0.722	1.15	0.68-1.95	0.598
Active	**Null**	23	13	0.72	0.67-1.55	0.413	0.70	0.29-1.63	0.410
Null	**Null**	29	18	0.80	0.40-1.57	0.519	0.91	0.44-1.90	0.819

* Crude OR ** Adjusted OR after controlling for family history of PE

Meta-analysis

A database according to the extracted information from each article was established. We identified 5 eligible studies (Zusterzeel et al., 2000; Cetin et al., 2005; Kim et al., 2005; Zhang et al., 2008; and present study), including 1217 subjects (515 patients, and 702 healthy controls) in relation to the study polymorphisms and risk of PE, which are summarized in Table 3. From these, 3, 1, and 1 study were carried out in Asian, European and American countries, respectively (Table 3). The numbers in the case-control studies varied considerably (range 55 to 351 individuals).

There was no significant heterogeneity between studies (Table 4). Our present meta-analysis indicated that there was no association between the *GSTT1* polymorphism and PE risk among all studies (OR=0.85, 95 % CI: 0.66-1.10, P=0.223). One study was reported from Korea (Kim et al., 2005), the participants in other studies were Caucasians (Zusterzeel et al., 2000; Cetin et al., 2005; Zhang et al., 2008; and present study). Excluding this study resulted a borderline association between *GSTT1* polymorphism and risk of PE (OR=0.73, 95 % CI: 0.53-1.01, P=0.054). The overall ORs of the PE risk were not associated with the *GSTM1* polymorphism among all studies (OR=0.99, 95 % CI: 0.78-1.25, P=0.955) or among Caucasians (OR=1.0, 95 % CI: 0.76-1.31, P=1.0).

Table 3: Studies used in the meta-analysis investigating the association between polymorphisms of *GSTM1* and *GSTT1* and risk of pre-eclampsia

Study	Country	Ethnicity	Control		Patients		OR	95 % CI	P-value
***GSTT1* polymorphism**			**Active**	**Null**	**Active**	**Null**			
Zusterzeel et al., 2000	Nether-lands	Caucasian	76	33	67	34	0.44	0.21-0.91	0.029
Kim et al., 2005	Korea	Asian	97	117	51	70	1.13	0.72-1.78	0.574
Cetin et al., 2005	Turkey	Caucasian	114	33	109	31	0.98	0.56-1.71	0.950
Zhang et al., 2008	USA	Caucasian	25	7	19	4	0.68	0.19-2.94	0.682
Current study	Iran	Caucasian	148	52	120	31	0.73	0.44-1.21	0.233
***GSTM1* polymorphism**			**Active**	**Null**	**Active**	**Null**			
Zusterzeel et al., 2000	Nether-lands	Caucasian	52	57	46	74	0.67	0.37-1.20	0.184
Kim et al., 2005	Korea	Asian	103	111	59	62	0.97	0.62-1.52	0.912
Cetin et al., 2005	Turkey	Caucasian	66	81	59	81	1.11	0.70-1.78	0.638
Zhang et al., 2008	USA	Caucasian	26	6	17	6	1.52	0.42-5.53	0.517
Current study	Iran	Caucasian	99	101	72	79	1.07	0.70-1.64	0.736

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Table 4: Summary of meta-analysis of case-control studies examining *GSTT1* and *GSTM1* polymorphisms and pre-eclampsia risk

Studies	Number of studies	Q-statistics	OR	95 % CI	P-value
***GSTT1* polymorphism**					
All studies	5	5.275	0.85	0.66-1.10	0.223
Caucasians	4	2.877	0.73	0.53-1.01	0.054
***GSTM1* polymorphism**					
All studies	5	2.530	0.99	0.78-1.25	0.955
Caucasians	4	2.520	1.0	0.76-1.31	1.0

DISCUSSION

Our present case-control study showed that family history of PE was significantly associated with elevated of PE risk, confirming previous reports (Robert and Cooper 2001; Sibai et al., 2005). We found that there was no significant association between smoking status and PE, which is not in agreement with previous reports (Robert and Cooper, 2001; Sibai et al., 2005). The discrepancy may be explained by very low prevalence of smokers among Iranian population. The observed prevalence for *GSTT1* and *GSTM1* null genotypes among control subjects were similar to other studies reported form Iran (Saadat et al., 2004a; Saadat and Farvardine-Jahromi, 2006; Saadat, 2006, 2007; Rafiee et al., 2010). Neither *GSTM1* nor *GSTT1* null genotypes were associated with risk of PE (Table 2). Our results are in concordance with previous studies investigating susceptibility to PE and genetic polymorphisms of *GSTM1* and *GSTT1* (Cetin et al., 2005; Kim et al., 2005; Zhang et al., 2008).

Previously it is reported that GSTs may have substrate overlapping (Hayes et al., 2005), also the additive effects of *GSTM1* and *GSTT1* polymorphisms on risk of several multifactorial traits were reported (Wilson et al., 2000; Saadat et al., 2004b; Saadat 2007; Masoudi et al., 2010). Therefore we investigate whether one null genotype could be compensated by an active genotype for the other isoenzymes, in further analysis we study the association between genotypic combination and risk of PE. There was no association between combination genotypes and risk of PE before and after adjustment for family history for PE.

The present finding from our case-control study showed that there is no evidence that one null genotype could be compensated by an active genotype for the other isoenzymes. This means that genetic polymorphisms of *GSTM1* and *GSTT1* are not risk factors for PE. It should be noted that there are many important risk factors for PE (Dekker and Sibai, 1998; Robert and Cooper, 2001; Moskovitz et al., 2002; Sibai et al., 2005; Chappell and Morgan, 2006; Chamy et al., 2006; Mütze et al., 2008) and in the present study we investigate only the possible confounding effect of family history on the association between GSTs polymorphisms and susceptibility to PE. Further investigations adjusting for confounding factors are needed to confirm the finding of the present study.

The studies investigating the association between *GSTT1* and *GSTM1* polymorphisms and susceptibility to PE are limited by small sample sizes (Zusterzeel et al., 2000; Cetin et al., 2005; Kim et al., 2005; Zhang et al., 2008), so there is a role for meta-analysis in pooling these studies, particularly to detect the small effect sizes that may be associated with these polymorphisms. There was no evidence of heterogeneity between studies used for meta-analysis. The present meta-analysis showed that neither *GSTT1* nor *GSTM1* polymorphisms were associated with susceptibility to PE. Finally it should be noted that the number of subjects, in the present meta-analysis is about 1217, which is much lower than the required samples. This warrants further investigation in larger studies.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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