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Genetic polymorphisms in metabolic enzymes and susceptibility to anti-tuberculosis drug-induced hepatic injury

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ABSTRACT. We examined the relationships between *N*-transacetylase 2 (NAT2), cytochrome P450 (CYP) 2E1 enzyme, glutathione *S*-transferase M1, T1 (GSTM1/GSTT1) gene polymorphisms, and anti-tuberculosis drug-induced hepatic injury (ADIH). A one-to-one matched case-control study was carried out using clinical data. *NAT2*, *CYP2E1*, *GSTM1*, and *GSTT1* polymorphisms were identified in 173 pairs of research subjects. Statistical analysis was performed to determine risk factors of ADIH. The results showed that low body mass index and alcohol consumption were risk factors of ADIH, with odds ratios of 6.852 and 3.203, respectively. The frequencies of *NAT2* slow acetylator, *CYP2E1* -1259G>C, -1019C>T wild-type, and the *GSTM1* null genotype were higher in the case group than in the control group, with odds ratios of 2.260, 2.696, 4.714, and 2.440, respectively. *GSTT1* was not found to be related to ADIH. Interactive analysis showed that *NAT2* slow acetylator and the *GSTM1* null genotype were mutually synergistic, while an antagonistic relationship was observed between

the *CYP2E1* wild-type genotype and the other 3 genetic types. The risks of hepatic injury were higher after anti-tuberculosis therapy in patients carrying the *NAT2* slow acetylator, *CYP2E1* -1259G>C, -1019C>T wild-type, and *GSTM1* null genotype.

Key words: Anti-tuberculosis drug-induced hepatic injury; Tuberculosis; Anti-tuberculosis therapy; Gene polymorphism; Metabolic enzyme

INTRODUCTION

Tuberculosis resulting from infection of *Mycobacterium tuberculosis* affects one-third of the world population. In 2010, more than 8.8 million people were diagnosed with tuberculosis (World Health Organization, 2011). Standard first-line anti-tuberculosis (anti-TB) chemotherapy regimens recommended by the WHO include isoniazid (INH), rifampicin, and pyrazinamide (World Health Organization, 2009), with an effective rate of 97%; however, these drugs show hepatotoxicity (Forget and Menzies, 2006). The hepatotoxicity of pyrazinamide was found to be higher than that of INH and rifampicin (Yee et al., 2003), with the negative effects amplified when the drugs are used together (Steele et al., 1991). Previous studies found that combination therapy of chemotherapy and anti-TB drugs increased hepatic injury by 2-28% (Durand et al., 1996; Tostmann et al., 2008); however, this rate varied widely by region. In extreme cases, patients may be forced to alter the chemotherapy regimen or even stop chemotherapy. Therefore, anti-tuberculosis drug-induced hepatic injury (ADIH) has prevented effective anti-TB therapy in some cases.

Hepatic injury occurs when toxic metabolites of drugs in the liver cannot be eliminated. In addition to environmental factors (Singla et al., 2010), drug metabolic enzymes play an important role in processes such as oxidation, deoxidation, hydrolysis of the phase I metabolic enzyme cytochrome P450 2E1 (CYP2E1), and catalysis conjugation reactions of the phase II metabolic enzymes *N*-acetyltransferase (NAT2), glutathione *S*-transferase M1 (GSTM1), and glutathione *S*-transferase T1 (GSTT1). NAT2 is classified into two groups depending on rapid acetylation and slow acetylation; wild-type NAT2 is a fast acetylator (Fretland et al., 2001), while two mutant alleles in the enzyme DNA sequence cause it to be a slow acetylator (Bell et al., 1993; Hein et al., 2000). Genetic polymorphisms influence INH metabolism (Sunahara et al., 1961). Studies in Taiwan, Japan, and Korea found that individuals carrying the *NAT2* slow acetylator variant had a higher risk of ADIH than those carrying the rapid acetylator form (Huang et al., 2002; Hiratsuka et al., 2002; Cho et al., 2007). CYP2E1 enzyme is a cytochrome P450 super-gene family member and contains at least 8 polymorphic loci. Among them, -1259G>C and -1019C>T are located in the 5'-end of the gene, and are closely related to CYP2E1 expression. Various studies have demonstrated that individuals carrying wild-type *CYP2E1* genes have a higher risk of developing ADIH (Huang et al., 2003), but a study in Korea found no relationship between *CYP2E1* genetic polymorphisms and ADIH (Vuilleumier et al., 2006). *GSTM1* and *GSTT1* are common polymorphisms; when there is a deletion mutation in homozygous genes, the corresponding enzyme loses activity, which further increases hepatotoxicity induced by anti-TB drugs (Bruhn et al., 1998).

A meta-analysis confirmed that polymorphisms in *CYP2E1*, *NAT2*, and *GSTM1* were related to ADIH (Sun et al., 2008), whereas the effects of different drug metabolic enzymes were mixed during ADIH (Fukino et al., 2008), as they showed either synergism or antago-

nism. In this study, we used a one-to-one matched case-control method to explore the relationships between metabolic enzyme gene polymorphisms of the 3 drugs and ADIH by examining the toxicity of drug metabolites and their detoxification process, as well as their interactions.

MATERIAL AND METHODS

Subjects

The research subjects were pulmonary tuberculosis patients of Han ethnicity diagnosed as eligible to participate in the study by Tangshan Tuberculosis Hospital between August 2010 and December 2011. A total of 173 pairs of subjects were included in this one-to-one matched case-control study. The study was approved by the Ethics Committee of Hebei United University (Document code: 10-007) and written informed consent was obtained from all enrolled patients.

Selection of cases

The cases were selected based on liver functions, i.e., all indices of liver function were normal before anti-TB chemotherapy, and became abnormal indicating hepatic injury after 6 months of chemotherapy. "Hepatic injury" was defined according to the American Thoracic Society criteria (Saukkonen et al., 2006), excluding those with abnormal liver function before chemotherapy. For drug-induced liver disorders, cases were patients who showed anti-TB drug-induced hepatitis based on increased serum transaminase values that were 3-fold higher than the normal upper limit (40 IU/L alanine aminotransferase) and symptoms compatible with hepatitis.

Selection of controls

In this one-to-one matched case-control study, the controls underwent the same anti-TB chemotherapy with the selected cases and were not tested with abnormality in liver functions after 6 months of the chemotherapy. The controls selected matched the criteria compared to the cases: i) same gender; ii) age discrepancy of less than 5 years; iii) living in the same regions; and iv) treatment with anti-TB drug regimens at the usual dosage, including 300 mg/day INH, 450 mg/day rifampicin, and 1500 mg/day pyrazinamide. Other disposal and exclusion criteria for the control group were the same as those used in the cases.

Epidemiological survey

A face-to-face interview was conducted to determine the subjects' marital status, occupations, body mass index, degree of addiction to alcohol and tobacco, medical history, prior/concomitant medications, anti-TB chemotherapy regimen, and results of liver function tests before and after medications. Conditional logistic regression was applied to measure the associations between subjects' characteristics and ADIH.

Genotype identification

Three milliliters of peripheral venous blood was drawn from fasted subjects for liver

function tests. Another 2 mL blood containing ethylenediaminetetraacetic acid for anticoagulation was stored at -70°C. Genomic DNA was extracted from 500 μL frozen whole blood by column chromatography. Polymorphisms at the 481C>T, 590G>A, and 857G>A loci of the *NAT2* gene, -1259G>C and -1019C>T loci of the *CYP2E1* gene, and the genes *GSTM1* and *GSTT1* for all subjects were analyzed by Tian Gen Biotechnology (Beijing, China) using DNA sequencing.

The mutated alleles from the loci 481C>T, 590G>A, and 857G>A of the *NAT2* gene are represented as M1, M2, and M3, and the wild-types are represented as WT. The 4 alleles of *NAT2* constituted 10 genotypes, including WT/WT, WT/M1, WT/M2, WT/M3, M1/M1, M1/M2, M1/M3, M2/M2, M2/M3, and M3/M3. Based on Bell et al. (1993), the subjects were classified as rapid and slow acetylators, with individuals containing 2 mutant alleles defined as slow acetylators and those containing at least 1 WT allele defined as rapid acetylators.

Statistical analysis

Conditional logistic regressions were conducted for univariate or multivariate analyses using SPSS 14.5 (SPSS, Inc., Chicago, IL, USA). Dichotomy analysis was applied to observe the interactions between gene locus polymorphism of the drug metabolic enzyme. Bonferroni's correction was used for two-sided tests with an inspection level of $\alpha = 0.025$.

RESULTS

Basic characteristics of the subjects

Among the 173 pairs of cases and controls, 118 pairs were males and 55 pairs were females. The average age was 48.8 ± 19.2 years (range, 15-88 years) in the case group and 48.6 ± 19.3 years (range, 17-85 years) in the control group. A total of 110 pairs were from rural areas and 63 were from urban areas. Hepatic injuries after anti-TB chemotherapy within the first, second, and third months were observed in 113, 41, and 19 patients, respectively, indicating that 89% of hepatic injuries occurred in the first 2 months of chemotherapy. No hepatic injury was found after 3 months of chemotherapy.

Factors associated with ADIH

The results showed that marital status, degree of education, occupation, and tuberculosis type did not significantly differ between the 2 groups, whereas body mass index and drinking status significantly differed in the single-factor analyses (Table 1).

Gene polymorphisms and ADIH

Single-factor and multiple-factor analyses of ADIH and gene polymorphisms

Analysis of Hardy-Weinberg equilibrium showed that the goodness of fits of genes *NAT2*, *GST*, and *CYP2E1* were excellent, with P values higher than 0.10, demonstrating that the control populations were in equilibrium and that the sample populations were representative of the larger population.

Single-factor logistic regression analysis indicated that the risks of hepatic injury af-

ter anti-TB chemotherapy for individuals carrying the slow acetylator variant were 2.26-fold higher than in individuals carrying the rapid acetylator form. The -1259G>C and -1019C>T wild type of the *CYP2E1* gene and the *GSTM1* null genotype were related to ADIH, although the null genotype difference of *GSTT1* in the 2 groups was not statistically significant (Table 2).

Table 1. Single-factor logistic regression analysis of anti-tuberculosis drug-induced hepatic injury-influencing factors.

Factors	β	SE	Wald χ^2	P	OR	95%CI
Marital status	0.456	0.377	1.461	0.227	0.634	0.302-1.328
Degree of education	-0.489	0.255	3.675	0.055	0.614	0.372-1.011
Occupation	0.233	0.198	1.394	0.238	1.263	0.857-1.860
Body mass index	1.925	0.531	13.118	0.001	6.852	2.418-19.413
Smoking status	0.271	0.331	0.671	0.413	1.311	0.6865-2.508
Drinking status	1.164	0.397	8.576	0.003	3.203	1.470-6.980

Table 2. Genotype of *NAT2*, *CYP2E1*, and *GST* associated with anti-tuberculosis drug-induced hepatic injury.

Controls	Cases		Wald χ^2	P	OR	95%CI
	Slow acetylator of *NAT2*	Rapid acetylator of *NAT2*				
Slow acetylator of *NAT2*	13	19	7.999	0.005	2.260	1.265-3.654
Rapid acetylator of *NAT2*	43	98				
	CYP2E1 -1259G>G	*CYP2E1* -1259C>C+G>C				
CYP2E1 -1259G>G	74	23	16.497	0.000	2.696	1.670-4.350
CYP2E1 -1259C>C+G>C	62	14				
	CYP2E1 -1019C>C	*CYP2E1* -1019T>T+C>T				
CYP2E1 -1019C>C	76	14	27.770	0.000	4.714	2.648-8.392
CYP2E1 -1019T>T+C>T	66	17				
	GSTM1 null	*GSTM1* WT				
GSTM1 null	15	24	14.109	0.001	2.440	1.532-3.886
GSTM1 WT	64	70				
	GSTT1 null	*GSTT1* WT				
GSTT1 null	31	40	1.323	0.250	1.275	0.843-1.929
GSTT1 WT	51	51				

To prevent interference among studied factors and to control for potential confounding factors, multiple-factor analysis was carried out using significant factors in the single-factor analysis as covariates (Table 3). Multiple-factor logistic regression analysis showed that after adjusting for body mass index and alcohol consumption, the *NAT2* slow acetylator, *CYP2E1* -1259G>C and -1019C>T wild type, and *GSTM1* null type were still significantly correlated with ADIH, with odds ratios (ORs) and 95% confidence intervals (95%CIs) of 2.146 (1.212-3.801), 2.541 (1.529-4.221), 5.115 (2.728-9.953), and 2.686 (1.607-4.491), respectively.

Interactive analysis of gene locus polymorphism

Based on the genotype characteristics of the subjects, dichotomy analysis was performed to explore the relationships between interactions of different genotypes of various metabolic enzymes and ADIH. The results showed that in phase II metabolic enzyme genes, synergism existed between the *GSTM1* null genotype, *NAT2* slow acetylator, and *GSTT1* null

genotype, with interaction coefficients of 6.021, 3.894, and 1.316, respectively. A super-multiplication effect was observed between the *GSTM1* null genotype and *NAT2* slow acetylator, and a secondary multiplication between *GSTT1* null genotype with *GSTM1* null genotype and *NAT2* slow acetylator. There was also an interaction between the phase I metabolic enzyme and phase II metabolic enzyme genes *NAT2*, *GSTM1*, and *GSTT1*. Among subjects carrying the *CYP2E1* mutant genotype and *NAT2* slow acetylator phenotype, the ORg_1 of ADIH was 6.382, while for subjects carrying the *CYP2E1* WT genotype and *NAT2* slow acetylator type, the ORg_1g_2 of *NAT2* decreased to 3.619, indicating that the *CYP2E1* genotype had receding effects on the *NAT2* slow acetylator (r = 0.705). In addition, antagonism existed between the *CYP2E1* WT genotype and *GSTM1* null genotype (OR = 6.625, 95%CI = 2.517-15.437) and *GSTT1* null genotype (OR = 2.480, 95%CI = 1.314-5.017). The interactions between these genes were all secondary multiplication effects.

Table 3. Multiple-factor logistic regression analysis associated with anti-tuberculosis drug-induced hepatic injury.

Model	Variable names	$\hat{\beta}$	SE	Wald χ^2	P	OR	95%CI
NAT2 acetylator	Rapid acetylator					1.000 (ref.)	
	Slow acetylator	0.764	0.292	6.857	0.009	2.146	1.212-3.801
	Body mass index	1.912	0.539	12.597	0.000	6.670	2.355-19.644
	Drinking status	1.353	0.377	12.904	0.000	3.867	1.849-8.089
CYP2E1 -1259G>C	G>G					1.000 (ref.)	
	G>C+C>C	0.932	0.259	12.962	0.000	2.541	1.529-4.221
	Body mass index	1.879	0.515	13.317	0.000	6.545	2.386-17.954
	Drinking status	1.210	0.393	9.457	0.002	3.353	1.551-7.249
CYP2E1 -1019C>T	C>C					1.000 (ref.)	
	C>T+T>T	1.632	0.321	25.882	0.000	5.115	2.728-9.953
	Body mass index	2.099	0.536	15.306	0.000	8.154	2.850-23.331
	Drinking status	1.245	0.423	8.687	0.003	3.474	1.518-7.954
GSTM1	*GSTM1* wild					1.000 (ref.)	
	GSTM1 null	0.988	0.262	14.197	0.000	2.686	1.607-4.491
	Body mass index	2.007	0.526	14.584	0.000	7.440	2.656-20.840
	Drinking status	1.381	0.396	12.166	0.000	3.977	1.831-8.639
GSTT1	*GSTT1* wild					1.000 (ref.)	
	GSTT1 null	0.165	0.232	0.510	0.475	1.180	0.749-1.858
	Body mass index	1.912	0.518	13.622	0.000	6.768	2.452-18.685
	Drinking status	1.291	0.379	11.638	0.001	3.637	1.732-7.638

DISCUSSION

Patients commonly respond to the same anti-TB chemotherapy regimen differently, both in terms of efficacy and side effects. Thus, physicians may face challenges in choosing an appropriate chemotherapy regimen for individual patients.

The frequently used first-line anti-TB drugs show varying degrees of hepatotoxicity. Hepatic injury occurs when toxic metabolites of these drugs in the liver cannot be made less toxic. However, patients with hepatic injury may also have other diseases causing abnormal liver function, such as viral hepatitis, alcoholic liver disease, autoimmunity hepatitis, hypoxia, bacteremia, and congestive heart-failure. In addition, drugs such as antibiotic chloramphenicol, analgesic-antipyretic, paracetamol, and the antipsychotic drug chlopromazine may cause abnormal liver functions.

This one-to-one matched case-control study excluded influences caused by relevant factors such as age and gender. In addition, we used a matching design for the chemotherapy

programs, whose efficiencies of both research design and statistical tests were higher than similar studies in the past.

As one of the important members of the P450 family, CYP2E1 participates in the metabolism of various drugs. Under the inhibitory action of INH, the enzymatic activity of WT CTP2E1 is higher than that of the mutant type and produces more metabolism with higher hepatotoxicity, increasing the risk of drug-induced hepatic injury. Therefore, phase I metabolic enzymes of CYP2E1 contribute to liver toxicity. CYP2E1 activities are normally distributed in the general population; however, nonconformity has been observed in both domestic and overseas studies, due to apparent racial differences. Studies have shown that the WT genotype of tuberculosis patients of Han nationality in the case group was higher than that in the control group, which agrees with the results of Vuilleumier et al. (2006), Lee et al. (2010), and Wang et al. (2010). A study conducted by Huang et al. (2003) showed that risks of hepatic injury in individuals carrying the WT genotype were 2.38-fold higher than in those carrying mutant genes, while studies in Korea and Brazil showed no evidence of significant differences between patients with the WT and mutant gene (Cho et al., 2007; Teixeira et al., 2011).

NAT2 is a phase II metabolic enzyme; however, the role of *NAT2* polymorphisms in ADIH is not consistent, as genotype distributions vary by region and race, and studies in the field hold different standards for hepatic injury. The risk of hepatic injury in individuals carrying *NAT2* slow acetylators was 2.26-fold higher than in those carrying rapid acetylators. These results are consistent with those of studies conducted in Taiwan (Huang et al., 2002; Lee et al., 2010), Tunisia (Ben et al., 2012), Brazil (Teixeira et al., 2011), and Iran (Khalili et al., 2011), but differ from those of studies conducted in the USA, which showed the opposite conclusion that the hepatotoxicity of rapid acetylators was higher than that of slow acetylators (Mitchell et al., 1975); this suggests that discrepancies may be due to differences in race.

GST is a superfamily of drug-metabolic enzymes, and includes various types of isoenzymes. The main functions of these enzymes are to catalyze and deoxidate glutathione and chemical structure-versatile electrophilic compounds by converting polar eletrophilic compounds into nonpolar hydrophilic compounds for elimination from the body, thus playing a role in detoxification. The frequencies of *GSTM1* and *GSTT1* null genotypes among different races and in different regions fluctuate between 21 and 100% and between 11 and 64.4%, respectively (Nelson et al., 1995). In this study, the frequency of the *GSTM1* null genotype in the case group was 2.44-fold higher than that in the control group, and no statistical difference was found in the distribution of *GSTT1* gene locus polymorphisms between the 2 groups. The results are consistent with those of Roy et al. (2001) in an Indian population.

A synergetic interaction was observed between the phase II metabolic enzyme *GSTM1* null genotype, *NAT2* slow acetylator, and *GSTT1* null genotype according to interactive analysis. The *GSTM1* null genotype modifies the hepatic injury effect of the *NAT2* slow acetylator and *GSTT1* null genotype, as well as amplifies the effect of the *GSTT1* null genotype to a NAT2 slow acetylator; however, an antagonistic relationship was observed between the phase I metabolic enzyme gene *CYP2E1* and the phase II metabolic enzyme genes *NAT2, GSTM1*, and *GSTT1*, indicating that the *CYP2E1* WT genotype weakens the effect of NAT2 slow acetylator. Thus, genotyping improves the understanding of drug enzyme metabolic capacity, providing guidance for physicians in selecting less hepatic toxic anti-TB drugs.

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