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# ASSOCIATION OF GSTT1 AND GSTM1 POLYMORPHISM WITH ANTI TB DRUG INDUCED HEPATOTOXICITY.

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**Abstract**

Combined therapy is used for the treatment of tuberculosis, which includes Isoniazid, Pyrazinamide and Rifampicin. It has been reported that Glutathione-S- transferases play an important role in elimination of toxic reactive metabolites of anti-tuberculosis drugs produced via cytochrome's metabolism. Inter individual variation to hepatotoxicity may be due to polymorphism in these genes. This candidate gene case-control study was carried out in 2019 to investigate the association of GSTT1 and GSTM1 polymorphism with hepatotoxicity. 243 patients were recruited for the study, in which 132 were cases and 111 were controls. Polymerase chain reaction based detection method was used to study polymorphism. The study indicated that GSTM1 and GSTT1 null genotypes may not be associated with hepatotoxicity (p=0.9, p=0.8). However, multi drug resistance is significantly associated with hepatotoxicity (p=0.0001, OR=7.9). Also, GSTT1 null genotype may be associated with multi drug resistance (p=0.01, OR=2.12). It is concluded that due to diminished activity of GSTs enzymes hepatotoxic intermediates are not further detoxified, causing hepatotoxicity. So it can be inferred that GSTT1 null genotype may be associated with hepatotoxicity in MDR TB patients.

**Index Terms:** GST, GSTT1, GSTM1, Tuberculosis, Hepatotoxicity, Anti-TB Drugs, Anti-TB Drug Induced Hepatotoxicity

## 1. INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis,* is the 2nd leading cause of death after HIV. One third of the world population has been suffering from tuberculosis

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infection and is a life threatening disease commonly attacking people of age 15 to 60 years [39]. Pakistan is ranked 6$^{th}$ among the 22 high burden countries of TB infection in WHO report 2013 [39]. The most common and conventional short-course TB treatment combination is two months use of rifampicin, isoniazid, pyrazinamide, ethambutol, followed by four months use of rifampicin and isoniazid. Side effects of these drugs, limits the clinical use of these drugs and contribute to treatment relapse and the appearance of multi drug resistant MTB strains [12, 10]. The most common and severe side effect of these drugs is hepatotoxicity [12, 31]. INH is mainly responsible for hepatotoxicity due to formation of toxic intermediates [34, 35]. These severe side effects may lead to serious injury or death [9].

Although the exact mechanism of anti TB drug induced hepatotoxicity (ATDIH) is unclear, it has been suggested that drug detoxifying enzyme coding gene polymorphism may increase the risk of hepatotoxicity due to ATDIH [36]. Among these metabolizing enzymes, GSTs are involved in TB drug metabolism [32]. INH is converted into hydrazine, acetyl hydrazine, acetylonium ion, acetyl diazine by NAT2 and CYP450 enzymes, which cause hepatotoxicity [29, 13]. GST enzymes are drug metabolizing enzymes, act as intracellular free radical scavenger, and conjugate glutathione with toxic metabolites produced from CYP2E1 metabolism. Then sulfhydryl conjugates with these metabolites and reduces their toxic effect by elimination from the body [29].

On the basis of nucleotide/amino acid sequence identity, physical structure of the genes and immuno-reactivity properties, human cytosolic GST genes have been classified into eight gene families encoding soluble GST protein; mu located on chromosome 1p and its size is about 5000bp, sigma located on chromosome 4q,alpha located on chromosome 6p and composed of seven exons having size of 11-12kb,Chi located on chromosome 10q,zeta on chromosome 14q and consisting of nine exons, theta on chromosome 22q, consisting of two genes, which have similar structures, being composed of five exons, Pi on chromosome 11q while the kappa's chromosomal location is unknown [16, 17]. It has been reported in some studies that genetic polymorphism in GSTM1 and GSTT1 is associated with high risk of TB drug induced hepatotoxicity [16]. Polymorphism has been reported to be high in a hepatotoxic patient having GSTT1 null polymorphism [27]**.** However**,** some studies resulted in observing no significant association of GST genes with anti TB drug induced hepatotoxicity [6, 33]. Due to these studies, conclusions are controversial and require other studies in various populations. As a result a candidate gene case-control study was carried out to generate data on the Pakistani population. The objectives of the study was to find out the association of GSTT1 and GSTM1 null genotypes with anti-TB drug induced hepatotoxicity and genetic marker identification for the prediction of ATDIH susceptibility for better management and control of TB. This the first case-control study to identify GST gene polymorphism, a possible genetic risk factor in the development of ATDIH, in Pakistani population.

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## MATERIALS AND METHODS:

This was a candidate gene case-control study in which 243 TB patients were recruited from six different hospitals: Muhammad Hussain Government TB Sanitorum Samli Muree, Rawalpindi Leprosy Hospital, National TB Control Dir Lower, TB hospital Baghdada (Mardan), District TB Control Office (Mardan), DHO Dargai (Malakand) and Lady Reading Hospital (Peshawar). Demographic and clinical history such as gender, weight, height, smoking history, socio-economic history, types of TB on the basis of treatment and ALT levels were recorded through structured questionnaire to evaluate the susceptibility and risk factors. This study was approved by Research Ethics Committee and written consent was obtained for all enrolled patients. Patients meeting the following Inclusion criteria were included in this study: diagnosis of active tuberculosis by clinical evaluation, diagnosis by radiology and microbiology testing. These patients were on antituberculosis therapy. Exclusion criteria of these patients were presence of liver diseases, viral hepatitis, history of intake of hepatotoxic drug and alcoholism. In 243 TB patients, 111 TB patients had normal ALT levels (7-55), which were taken as a control while 132 patients had high ALT level>65, indicating hepatotoxicity.

### Determining GSTT1 and GSTM1 genotypes:

DNA was isolated from the blood using phenol-chloroform method. GSTT1 and GSTM1 genotyping was carried out by multiplex PCR, in which beta globulin was used as internal control (8). Primers used for amplification were. Amplification was performed using a thermal cycler (T personal ThermoCycler, Biometra, Germany). PCR was performed by preparing 20µl reaction mixture contained 1.25U Taq polymerase (Invitrogen), 10x PCR buffer (100mMTris-HCl, pH 8.3, 500mM $(NH_4)_2SO_4$, 1.5mM MgCl2, 10pmol/µl each primer, and 40ng DNA. Conditions used for amplification were: initial denaturation at 95 C for 5 minutes, followed by 39 cycles of denaturation at 95C for 45 s, annealing at 57C for 55 s, extension at 72C for 5 minutes, followed by additional final extension at 72C for 10 minutes.

### Results:

Out of 243 TB patients, 132 had higher ALT than normal showing evidence of hepatotoxicity were selected as cases while 111 TB patients which had normal ALT level, were selected as controls.

In the absence of GSTT1, GSTM1 and beta globulin, bands of 459bp, 215bp and 268bp were seen on 2% agarose gel as shown in figure 1.

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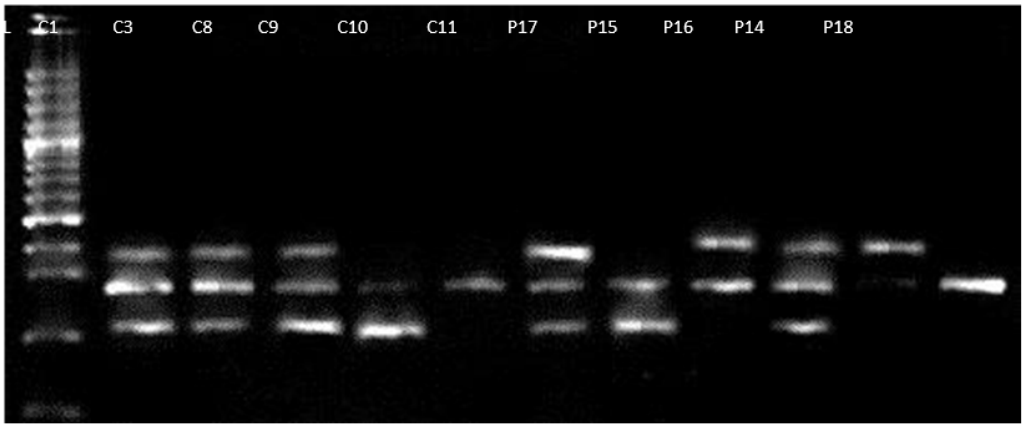


**Figure 1: : Ethedium bromide stained 2% agarose gel showing amplified product of GSTT1, GSTM1 and beta globulin genes with 100bp ladder(Invitrogen) on the right (1st lane).Lanes (2-6) shows 459bp bands of GSTT1, 215bp bands of GSTM1 and 268bp of beta globulin in controls, while lanes (7-11) shows bands in TB Patients.**

The demographic features of case and controls are shown in table 2.

There was no significant difference in age, gender, marital status, BCG vaccination and smoking history between cases and controls, showing no association of these demographic features with hepatotoxicity as shown in table 1. However the number of MDR TB patients having high ALT, are greater (82.9%) than MDR TB patients having normal ALT levels (17.1%), which indicates a significant association with hepatotoxicity. GSTT1 null genotypes are present in 64.39% cases and 63.06% controls, showing no association with hepatotoxicity. There was no difference in GSTM1 null genotypes between cases (76.51%) and controls (75%). The simultaneous occurence of both GSTT1 and GSTM1 null genotypes was 53.03% in patients, while it was 52.25% in controls (p=0.9), showing no association of these genotypes with hepatotoxicity. There was no difference in GSTM1 null genotypes between MDR (71.5%) and new cases (70.08%). In MDR, both GSTM1 and GSTT1 null genotypes were more (50%) as compared to new cases (39.51%), but the data is statistically not significant (p=0.1, OR=1.53) as shown in table 3. In MDR, GSTT1 null genotypes were more (67.04%) as compared to new cases (48.95%) and the data is also statistically significant (p=0.01, OR=2.12). In MDR GSTT1, null genotypes were two folds greater as compared to new cases, showing significant association of GSTT1 null genotype with multi drug resistance to anti TB drugs, as shown in table 4.

## DISCUSSION:

Combined therapy is usually used in the treatment of TB to get better results. These drugs include Isoniazid, rifampicin, and pyrazinamide. However, it is known that these drugs may be responsible for induction of hepatotoxicity. Earlier studies show that

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genetic factors are also involved in drug induced hepatotoxicity. Several studies carried out on TB association with GSTT1 and GSTM1 polymorphism have reported that null genotypes of these genes are associated with TB drug induced hepatotoxicity [13,28]. In Taiwanese and Indian population, also a significant association between GSTM1 null genotypes and TB drug induced hepatotoxicity was found [19, 28]. However, other studies by Suarez-Kurtz *et al*., 2007, Tang *et al*., 2012, and Figueiredo-Teixeira *et al*., 2011 have reported contradictory results, showing insignificant association between GSTT1 and GSTM1 null genotypes to anti-TB drugs induced hepatotoxicity.

There was no difference in GSTM1 null genotypes between cases and controls, indicating absence of any association of GSTM1 null genotype with drug induced hepatotoxicity, which is in line with earlier studies carried out on Korean, Brazilian and Caucasian population; $p>0.05$, $p=0.06$, $p>0.05$ respectively [8, 21, 24], but contradicts with studies carried out on Indian, Taiwanese and Western Indian populations; $p=0.05$, $p=0.05$, $p<0.05$ [13, 19,29]. No significant difference was found in GSTT1 null genotypes among cases and controls ($p=0.8$), showing no association of GSTT1 null genotype and hepatotoxicity which support earlier studies carried out on Indian, Brazilian, Taiwanese, Western Indian and Korean populations; $p>0.05$, $p=0.9$, $p>0.05$, $p>0.05$, $p=0.05$ [13,8,19,29]. However, a study carried out on Caucasians [24], had yielded results contrary to our findings, where a significant relationship ($p=0.03$), had been reported. Simultaneous presence of GSTT1 and GSTM1 null genotype in our study was 53% in cases and 52% in controls but, the data is statistically insignificant (0.9), indicating no association of these genotypes with hepatotoxicity.

Multi drug resistance was significantly associated with hepatotoxicity (OR=7.91, $p=0.001$). Hepatotoxicity was seven folds more in MDR TB patients, which is not reported in early studies carried out in Korean, Caucasian, Brazilian, Taiwanese and Indian populations. Also GSTT1 null genotypes were more in MDR TB patients (67.04%), as compared to newer TB cases (48.95%), the differences being statistically significant (OR=2.01, $p=0.01$). Incidence of GSTT1 null genotype was two folds higher in MDR patients as compared to new cases, suggesting that GSTT1 null genotype may be associated with multi drug resistance. In TB drug metabolism, along with GSTs, other enzymes like N-acetyl transferases and cytochrome proteins are also involved. Earlier studies reveal that pyrazinamide causes up regulation of cytochrome expression. As a result of overexpression of cytochrome, early detoxification of TB drugs occurs before action, by converting into hepatotoxic intermediates and due to diminished activity of GSTT1 enzymes, these are not further detoxified, causing hepatotoxicity. However, further studies on candidate genes need to be performed with other drug metabolizing enzymes, to confirm these predictions.

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## APPENDICES

### Table 1: Primers used for GSTT1, GSTM1 and beta globulin genes amplification

| Primer | Forward | Reverse |
|---|---|---|
| GSTT1 | 5-GAAGTCCTGCTTATGCTGCC-3 | 5-GGCGAGAGAGCAAGACTCAG-3 |
| GSTM1 | 5-GAACTCCCTGAAAAGCTAAAGC-3 | 5-GTTGGGCTCAAAT ATACGGTGG-3 |
| Beta globulin | 5-GAAGAGCCAAGGACAGGTAC-3 | 5-CCACTTCATCCACGTTCACC-3 |

### Table 2: Demographic and clinical features of patients and controls and their association with hepatotoxicity

| Demographic features | Cases (%) | Controls %) | χ2 | OR | 95%CI | P value |
|---|---|---|---|---|---|---|
| Females | 52.0 | 47.0 | 0.225 | 0.88 | 0.53-01.46 | 0.60 |
| Males | 55.7 | 44.2 | 0.22 | 1.13 | 0.68-01.87 | 0.63 |
| BCG vaccinated | 53.4 | 46.5 | 0.02 | 0.95 | 4.16-15.06 | 0.87 |
| Smokers | 45.8 | 54.1 | 0.73 | 0.69 | 0,29-0161 | 0.30 |
| Married | 51.3 | 48.6 | 0.002 | 0.99 | 0.51-01.90 | 0.98 |
| Unmarried | 51.4 | 48.5 | 0.0002 | 1.00 | 0.52-1.92 | 0.98 |
| Age Adolescent | 53.2 | 46.9 | 0.019 | 1.04 | 0.55-01.95 | 0.80 |
| Young adults | 55.4 | 44.5 | 0.197 | 1.12 | 0,67-01.88 | 0.66 |
| Adults | 56 | 43.1 | 0.135 | 1.13 | 0.58-02.18 | 0.71 |
| MDR | 82.9 | 17 | 45.58 | 7.91 | 4.16-15.06 | 0.001 |

### Table 3: GSTT1 and GSTM1 genotyping frequency among cases and controls

| Genotyping | Cases (%) | Controls (%) | χ2 | OR | 95%CI | P value |
|---|---|---|---|---|---|---|
| GSTT1 null genotypes | 64.39 | 63.06 | 0.0001 | 1.05 | 0.62-1,79 | 0.82 |
| GSTM1 null genotypes | 76.51 | 75.0 | 0.04 | 0.99 | 0.54-1.80 | 0.99 |
| Both GSTT1 and GSTM1 null genotypes | 53.03 | 52.25 | 20.01 | 1.03 | 0.62-1.71 | 0.9 |

### Table 4: GSTT1 and GSTM1 genotyping frequency among MDR and new TB cases

| Genotyping | MDR (%) | New Cases (%) | χ2 | OR | 95%CI | P value |
|---|---|---|---|---|---|---|
| GSTT1 null genotypes | 67.04 | 48.95 | 6.16 | 2.12 | 1.16-3.85 | 0.01 |
| GSTM1 null genotypes | 71.59 | 70.8 | 0.02 | 1.03 | 0,54-1.96 | 0.9 |
| Both GSTT1 and GSTM1 null genotypes | 50 | 39.58 | 2.016 | 1.52 | 0.85-2.73 | 0.1 |

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