

# Correlation of GSTM1 gene deletion in joint synovial fluid with the recovery of patients undergoing artificial hip replacement

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**Abstract.** The present study was designed to investigate the correlation between glutathione S-transferase M1 (GSTM1) gene polymorphism and the recovery of patients undergoing artificial hip replacement. A total of 241 patients including 149 males (61.8%) and 92 females (38.9%) who received artificial hip replacement in People's Hospital of Rizhao between December 2010 and October 2016 were enrolled to serve as the observation group. Patients were divided into two subgroups according to the loss of GSTM1. A total of 80 healthy subjects who underwent a physical examination in our hospital at the same period were selected to serve as the control group. The control group included 41 males (51.25%) and 39 females (48.75%). GSTM1 gene genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). All patients were followed up for 12 months. Clinical data were compared between the deletion and non-deletion groups and the hospitalization time and the length of the use of antibiotics were compared. Deletion rate of GSTM1 gene in the observation group was 67.63%, which was significantly different from that in the healthy control group [odds ratio (OR)=1.51, 95% confidence interval (CI): 1.075-2.023,  $P<0.05$ ]. Notably, a significant difference was indicated in the recovery between patients with and without GSTM1 gene deletion after a year discharged from hospital ( $P<0.05$ ). There was no significant difference according to sex, age, hypertension, smoking history, leukocyte, hemoglobin, platelet and BMI index between patients in deletion and non-deletion groups ( $P>0.05$ ). However, there was a significant difference in the number of patients with diabetes

between the two groups ( $P<0.05$ ). Hospitalization time and the length of antibiotics use were significantly longer in deletion group compared with non-deletion group ( $P<0.05$ ). Infection rate in the deletion group was significantly higher than that in the non-deletion group. Results suggested that GSTM1 gene polymorphism may be correlated with recovery of patients undergoing artificial hip replacement, and GSTM1 gene deletion may correlated with poor recovery.

## Introduction

With the growth of aging population, incidence of hip joint disease shows an increasing trend. Artificial hip replacement is a type of reconstructive operation that replaces the partial or integral damaged hip joint by adopting joint prosthesis fabricated by artificial simulation to ameliorate and restore the function of the hip joint, and is one of the major methods in the treatment of joint diseases in recent years (1-3).

Glutathione S transferases (GSTs) are an important family of phase II metabolic enzymes in the human body, and family members include GSTM1, GSTT1, and GSTP1 (4,5). A previous study (6), showed that GSTs can catalyze the sulfhydryl group of reduced glutathione to react the electrophilic compound to increase their water solubility for excretion, so as to play an important role in detoxification of carcinogens and metabolism of anticancer drugs. Genetic polymorphisms of GSTs can alter enzyme activity, thus increasing the risk of various diseases (6). A previous study (7) has shown that the missing genotypes of GSTM1 and GSTT1 can lead to loss of function of their encoded enzymes. Alteration of A313G (Ile105Val) on exon 5 of GSTP1 (rs1695) results in decreased thermal stability and reduced specific catalytic activity of the encoded protein. Changes in the polymorphisms of the three genes can affect the metabolism of chemotherapeutic drugs by the cells, resulting in differences in the effective plasma concentrations of chemotherapeutic agents, which ultimately leads to differences in efficacy, toxicity, and prognosis of chemotherapy (8). Currently, GSTs gene polymorphism has attracted more and more attentions. Previous studies have shown that glutathione S-transferase M1 (GSTM1) deletion may lead to the occurrence of some malignant tumors, such as lung cancer (9), liver cancer (10), gastric cancer (11) and

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nasopharyngeal carcinoma (12) and other tumors. A previous study (13), has reported that GSTs gene polymorphisms may lead to reduced antioxidant activity of enzymes, leading to increased susceptibility to diabetes. Another study showed that infection rate of diabetic patients is 3 times higher than that of non-diabetic patients after artificial hip replacement (14). However, the correlations between GSTM1 gene deletion and artificial hip replacement are still controversial. Hence, the present study investigated the correlation between GSTM1 gene deletion and recovery of patients undergoing artificial hip replacement.

## Materials and methods

**Basic data.** A total of 241 patients who received artificial hip replacement in People's Hospital of Rizhao from December 2010 to October 2016 were enrolled to serve as observation group. Those patients included 149 males (61.8%) and 92 (38.9%) females, and the mean age was  $65 \pm 9.41$  years. Eighty healthy people who at the same period took physical examination in our hospital were selected to serve as control group. Control group included 41 males (51.25%) and 39 females (48.75%). There were no statistically significant differences in sex, age, hypertension, diabetes and smoking history between two groups ( $P > 0.05$ ) (Table I). Harris scoring (15), which includes seven indexes: Pain (44 points), daily activity (14 points), gait (11 points), walking aid (11 points), walking distance (11 points), deformity (4 points) and the degree of activity (5 points) was performed with a total of 100 points. Four grades were set based on the total scores: 100-90, excellent; 89-80, good; 79-70, fair; <70, poor. All participants and their families signed informed consent. This study was approved by the Ethics Committee of People's Hospital of Rizhao (Shandong, China).

**Instrument and reagents.** TRIzol reagent and PCR 2X Taq MasterMix kit was purchased from Invitrogen; Thermo Fisher Scientific, Inc. (Waltham, MA, USA). DNA Marker was purchased from Sigma-Aldrich; Merck KGaA (Darmstadt, Germany). Roche light cycle 480 was purchased from Roche Diagnostics (Basel, Switzerland).

**Follow-up.** Patients were followed up once every month within the first three months after operation, followed by once every three months for nine months. Hospitalization time, the length of the use of antibiotics and the condition of infection were analyzed in deletion group and non-deletion group were recorded. After discharge from hospital, the patient continued to receive antithrombotic therapy, such as oral coumarin or aspirin, and the corresponding training, such as the constriction exercise of the affected limb, the continuous passive exercise, the training of joint motion, walking practice and stairs exercises were used to prevent postoperative complications.

**Exclusion and inclusion criteria.** Inclusion criteria: Patients received no hormone drug treatments; patients with normal liver and kidney function; patients willing to cooperate with researchers. Exclusion: Patients with rheumatism, rheumatoid arthritis or gonarthrosis; patients with mental illness or

physical disability; patients who were not willing to receive treatment.

**Collection of specimens and extraction of total ribonucleic acid (RNA).** Three milliliters synovial fluid was collected and transferred into a centrifuge tube, followed by centrifugation at  $2,500 \times g$  at  $4^{\circ}\text{C}$  for 10 min. Subsequently, the supernatant was transferred to a Eppendorf (EP) tube and restored at  $-80^{\circ}\text{C}$ . DNA was extracted according to the instructions of kit, followed by reservation at  $-20^{\circ}\text{C}$ .

**Single nucleotide polymorphism sequencing.** GSTM1 genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with  $\beta$ -globin as the endogenous control. Primer sequence of GSTM1 gene were: 5'-TACTCAGAGTTTCTGGGGAAGCGGC-3' (forward) and 5'-ACGGTGGAGGTCAAGGACATCATAG-3' (reverse); Primer sequences of endogenous control  $\beta$ -globin were: 5'-GAACCCAGGGTACAGAGAAAGATC-3' (forward) and 5'-GGACGAAGGAAGAGTGTCTCGGAAG-3' (reverse). PCR reaction system was  $25 \mu\text{l}$ :  $2 \mu\text{l}$  DNA template,  $0.5 \text{ mol/l}$  primer,  $2 \times 2.0 \mu\text{l}$  deoxy-ribonucleoside triphosphate (dNTP),  $2.5 \mu\text{l}$  buffer,  $1.5 \text{ mol/l}$   $\text{MgCl}_2$  and  $1.0 \text{ IU}$  TaqDNA. PCR reaction conditions were: Pre-denaturation at  $94^{\circ}\text{C}$  for 2 min, followed by 35 cycles of  $94^{\circ}\text{C}$  for 45 sec,  $55^{\circ}\text{C}$  for 50 sec and  $72^{\circ}\text{C}$  for 50 sec, and  $72^{\circ}\text{C}$  for 5 min. Finally,  $10 \mu\text{l}$  PCR product was subjected to electrophoresis by using 1.5% agarose gel for 45 min, followed by staining with 1.5% ethidium bromide (EB).

**Statistical analysis.** Data obtained in the present study were analyzed by using Statistical Product and Service Solutions (SPSS, Inc., Chicago, IL, USA) v.17.0 statistical software. Enumeration data were compared by Chi-square test. Measurement data were expressed by mean  $\pm$  SD. t-test was used for the comparisons between deletion and non-deletion groups.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**PCR amplification results.** Multiplex PCR amplification of GSTM1 was carried to obtain products with a length of 298, 248 and 207 bp. GSTM1 (-) genotype only showed a band of 298 bp, while GSTM1 (+) showed two bands after electrophoresis (Fig. 1).

**GSTM1 gene polymorphism and recovery of patients undergoing artificial hip replacement.** In the present study, there were 241 patients with artificial hip joint replacement. Gistcontinuous chi-square test showed that GSTM1 gene deletion type in observation group (67.63%) was higher than that in control group (41.25%), suggesting that deletion of GSTM1 gene is related to the poor recovery of patients undergoing artificial hip replacement (OR=1.51, 95% CI: 1.075-2.023,  $P < 0.05$ ; Table II).

**Comparison of clinical data between deletion group and non-deletion group in experimental group.** Patients were divided into GSTM1-deletion and non-GSTM1-deletion

Table I. Basic data of two groups.

Factor	Experimental group (%)	Control group (%)	OR (95% CI)	$\chi^2$	P-value
Sex					
Male	149 (61.8)	41 (51.25)	1.51 (1.12-4.94)	0.814	0.574
Female	92 (38.9)	39 (48.75)			
Age (years)					
≥65	107 (44.39)	37 (46.25)	2.41 (1.71-3.44)	6.74	0.749
<60	134 (55.61)	43 (53.75)			
Hypertension					
Yes	170 (70.53)	33 (41.25)			
No	71 (29.47)	47 (58.75)			
Diabetes					
Yes	96 (39.83)	29 (36.25)	1.88 (1.08-2.98)	5.41	0.766
No	145 (60.17)	51 (63.75)			
Smoking history					
Yes	162 (67.21)	41 (51.25)	2.87 (1.74-3.04)	10.55	0.648
No	79 (32.79)	39 (48.75)			
White blood cells (10x9/l)	4.49±1.5	4.1±1.7		1.948	0.052
Hemoglobin (g/l)	162.5±26.40	169.6±33.00		1.485	0.138
Platelets (10x9/l)	132.0±25.14	138.0±25.20		1.849	0.065
BMI index (kg/m <sup>3</sup> )	22.51±1.30	22.78±1.15		1.655	0.099

Table II. GSTM1 gene polymorphism and recovery of patients undergoing artificial hip replacement.

Genotype	Experimental group, n=241 (%)	Control group, n=80 (%)	OR (95% CI)	$\chi^2$	P-value
GSTM1					
GSTM1 (+)	78 (32.37)	47 (58.75)	-		
GSTM1 (-)	163 (67.63)	33 (41.25)	1.51 (1.075-2.023)	0.743	<0.05

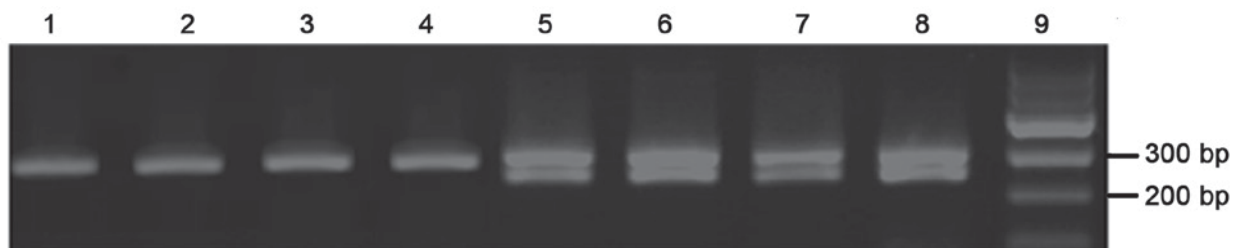


Figure 1. GSTM1 genotyping electrophorogram. Lanes 1, 2, 3 and 4: GSTM1 (-) genotypes; Lanes 5, 6, 7 and 8: GSTM1 (+) genotypes; Lane 9: Marker.

groups. we found that there was no difference in sex, age, hypertension, smoking history, leukocyte, hemoglobin, platelet, and BMI index between patients in deletion and non-deletion groups ( $P>0.05$ ). The number of patients with diabetes in GSTM1-deletion was more than that in non-GSTM1-deletion group ( $P<0.05$ ; Table III).

**Prognosis of patients.** Hospitalization time and the length of the use of antibiotics were compared between deletion group and non-deletion group. We found that hospitalization time

and the length of the use of antibiotics were significantly longer in deletion group than in non-deletion group ( $P<0.05$ ; Fig. 2). In addition, infection rate of deletion group was significantly higher than that of non-deletion group ( $P<0.05$ ; Table IV).

**Follow-up.** Observation group was divided in two groups including deletion group and non-deletion group, and all patients were followed up for 12 months. Harris scoring was performed. No significant differences in Harris scores were found between two groups on the day of discharge ( $P>0.05$ ).

Table III. Comparison of clinical data between deletion group and non-deletion group in experimental group.

Variables	Deletion (n=163)	Non-deletion (n=78)	t	P-value
Sex				
Male	100	49		0.887
Female	63	29		
Age (years)				
≥65	75	32		0.491
<65	88	46		
Hypertension				
Yes	120	50		0.134
No	43	28		
Diabetes				
Yes	77	19		0.001
No	86	59		
Smoking history				
Yes	115	47		0.142
No	48	31		
White blood cells (10x9/l)	4.84±1.76	4.61±1.24	1.037	0.301
Hemoglobin (g/l)	163.39±23.87	167.39±25.75	1.186	0.237
Platelet (10x9/l)	126.89±29.12	134.29±29.61	1.836	0.068
BMI index (kg/m <sup>3</sup> )	22.48±1.84	22.89±1.06	1.827	0.069

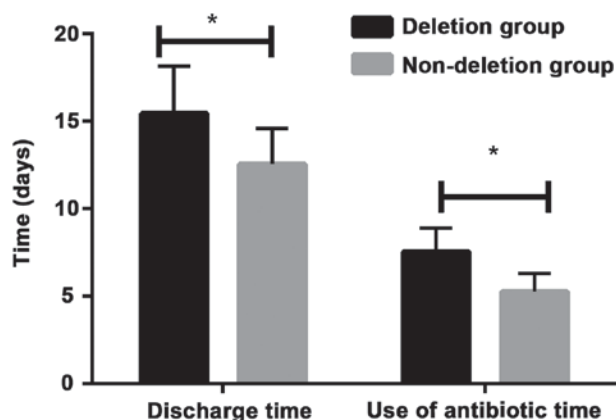


Figure 2. Comparison of hospitalization time and the length of the use of antibiotics between 2 groups. Hospitalization time and the length of the use of antibiotics were significantly longer in deletion group than in non-deletion group. \*P<0.05.

Harris scores were significantly lower in deletion group than those in non-deletion group half year (P=0.004) and one year after discharge (P=0.001; Table V).

## Discussion

In recent years, with the application of biological materials and maturation of surgical techniques, artificial hip replacement technique becomes more and more mature (16,17). At present, postoperative infection is still the main problem of artificial hip replacement, and has a great influence on the recovery of patients (18). Hence, in order to reduce postoperative

Table IV. Prognosis of patients.

Groups	Infection	Non-infection	P-value
Deletion (n=78)	37 (47.44)	41 (52.56)	0.048
Non-deletion (n=163)	55 (33.74)	108 (66.26)	

complications caused by artificial hip replacement and improve patient's quality of life, effects of GSTM1 polymorphism on the recovery of patients underwent artificial hip replacement was first investigated in the present study.

As an important phase II metabolic enzyme, GSTM1 is located on the first chromosome, which has detoxificative and cell protective effects to the human body (19,20). A large number of studies reported that (21-23) GSTM1 is associated with the occurrence and prognosis of various types of cancer, but its involvement in artificial hip replacement remains unclear. In the present study, PCR-RFLP technology was adopted to analyze the genotype deletion of GSTM1 gene, so as to study the recovery of patients undergoing artificial hip replacement.

Results of this study indicated that the distribution frequency of deletion type of GSTM1 gene was 41.25% in control group, which is consistent with the finding in previous study (24). Among 241 patients undergoing artificial hip replacement, there were 163 (67.63%) cases of deletion type of GSTM1 gene. Significant difference in distribution frequency was found between observation group and control group (OR=1.51, 95% CI: 1.075-2.023, P<0.05), suggesting that deletion of GSTM1 gene is correlated with poor recovery. Studies

Table V. Comparisons of Harris scores.

Group	n	Discharge after operation	Half a year after discharge	One year after discharge
GSTM1 gene deletion type	163	59.41±12.88	66.47±10.57	71.43±16.94
GSTM1 gene non-deletion type	78	60.57±14.38	70.76±11.67	79.12±15.51
t value		6.874	8.419	9.354
P-value		0.364	0.074	0.047

have shown that the absence of the GSTM1 gene may lead to the development of diabetes, and the incidence of infection in patients with diabetes after hip replacement is much higher than normal, delaying recovery and leading to poor prognosis. We compared the clinical data between the deletion group and the non-deletion group. We found that the number patients with diabetes in deletion group were significantly bigger than that in the non-deletion group. This also shows that there is a link between the loss of GSTM1 gene and the prognosis of hip replacement patients. Loss of GSTM1 gene may cause the development of diabetes, and the risk of infection in patients with diabetes after hip replacement is much higher than that in normal people. Therefore, patients were further divided into GSTM1 gene deletion group and GSTM1 gene non-deletion group for follow-up study. Harris score revealed that recovery of patients in GSTM1 gene deletion group was significantly worse compared with that in GSTM1 gene non-deletion group within one year after discharge ( $P<0.05$ ), indicating that GSTM1 gene deletion may be a risk factor for the delayed recovery in patients underwent artificial hip replacement. Those results indicate that GSTM1 gene deletion in patients with hip replacement had an impact on prognosis. Life safety and health issues are currently the focus of social attention. Recovery after artificial hip replacement is a slow and systematic process. Individualized treatment and rehabilitation can reduce the occurrence of complications after replacement, thus achieving better recovery effect to improve the quality of life of patients. This study provided references for the prediction of recovery of patients with artificial hip replacement.

It is the first time to make study through combining GSTM1 gene with artificial hip replacement. This study is hoped to provide better service for the recovery of patients and clinical treatment through discussing the relationship between GSTM1 gene and recovery of patients undergoing artificial hip replacement. Also an in-depth discussion will be made according to the results of this study and deeper-seated experiments will be designed according to the guess of influence mechanism in the future. There are also limitations in this study, for example, the short period of the follow-up and small sample size caused by the difficulty in enrolling healthy volunteers, in which may affects the reliability of the results. Future studies with bigger sample size are needed to further confirm the conclusions in the present study.

In conclusion, PCR-RFLP technology is successfully utilized to analyze GSTM1 genotypes in synovial fluid, and the results suggest that GSTM1 gene polymorphism is correlated with recovery of patients undergoing artificial hip replacement. The present study provided references for postoperative rehabilitation of patients undergoing artificial hip replacement.

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## Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

## Authors' contributions

XL and TX conceived and designed the study. XL and BH were responsible for the collection and analysis of the data. BW and MQ interpreted the data and drafted the manuscript. XL and BW revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study was approved by the Ethics Committee of People's Hospital of Rizhao (Shandong, China). Signed written informed consent was obtained from the patients and/or guardians.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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