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Association of Glutathione S-Transferase Gene Class T1 (GSTT1) and M1 (GSTM1) with Gastroesophageal Reflux Disease Severity and Diabetes Mellitus

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Abstract

Background & Aims: Glutathione S-transferase (GST) plays a key role in detoxification of xenobiotics and consequently polymorphisms of GST gene may determine susceptibility to several types of metabolic disorders and endue free radicals elimination. There is still no clear evidence of GSTM1 and GSTT1 genes association with gastroesophageal reflux disease (GERD) complication by diabetes mellitus type 2 (DM2). Therefore, the aim of the study is to establish the difference in null GSTM1 and GSTT1 genes polymorphisms between GERD patients with and without diabetes in Northern Bukovina (Western Ukraine).

Methods: The GSTM1 and GSTT1 genes' polymorphisms were analyzed using a multiplex polymerase chain reaction (PCR) in 33 patients with GERD and DM2 and 17 controls with GERD without DM2.

Results: It was found that there is no significant difference ($p>0.05$) in GSTM1/GSTT1 haplotypes distribution between observed groups. Neither GSTM1 null mutation, nor GSTT1 null mutation increase the risk of GERD and DM2 incidence, depending on types and severity of esophagitis (OR=0.48-2.03, 95% CI=0.06-8.66, $p>0.05$). Almost half (48.0%) of patients with GERD have mutation in the studied GST genes promoters areas. Every third patient (36.0%) is the carrier of a mutant 0/0-genotype of GSTM1 gene in haplotype, while the combination of homozygous GSTT1 gene mutations observed 2.6 times less often (14.0%). Linked mutation is absent in 52.0% of patients. No statistically significant associations were observed between the haplotypes of GSTM1 and GSTT1 genes and GERD/DM2 presence, depending on smoking, age, gender, and type of esophagitis.

Conclusion: Presence of homozygous deletion in the promoters' areas of GSTT1 and/or GSTM1 genes in haplotype does not significantly increase the risk of DM2 in GERD patients.

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Key words

gastroesophageal reflux disease; diabetes mellitus; GSTT1; GSTM1

Introduction

Gastroesophageal reflux disease (GERD) is an important common disease in with multi-factorial etiology, involving complex interactions between genetic and environmental factors, and individual susceptibility to environmental risk factors. This difference in susceptibility may result from inherited polymorphisms in various genes controlling enzymatic metabolism, detoxification processes, repair of DNA damage and cell cycle.[1-3] The glutathione S-transferases (GSTs) are genes of phase II metabolic enzymes superfamily that play the general function in conjugating glutathione with electrophilic substances capable of generating free radicals.[4] Also, they can be involved in the development of cardio-vascular diseases and diabetic mellitus complications,[5,6] alcoholic liver cirrhosis,[7] non-alcoholic fatty liver disease,[8] with conflicting data about their role in initiation of carcinogenesis,[9-11] determining peroxidase activity and inflammatory responses in patients with Rheumatoid Arthritis, etc.[12] GSTs genes mutations are associated with reduced activity of GSTs and are of great interest for determining the disease susceptibility.[13] The GSTs' isoenzymes are divided into at least five major classes (α, μ, π, θ, ζ).[14] Clinically significant polymorphisms have been detected in the genes encoding for GSTA1 (α class) GSTM1 (μ class), GSTP1 (π class), GSTT1 (θ class) and GSTZ1 (ζ class). Among them, the GSTM1, GSTP1 and GSTT1 genotypes have been extensively studied during recent years for their potential modulating role in individual susceptibility to environmentally-induced diseases. The GSTM1 gene in chromosome 1p13, GSTT1 gene in chromosome 22q11.2 – according to three alleles, can be grouped into two classes: GSTM1-null, GSTT1-null homozygote for the null allele (GSTM1-0, GSTT1-0) – nonfunctional class and GSTM1-1, with at least one of the GSTM1a, or GSTM1b alleles, or GSTT1-

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1 – functional class.[15] Polymorphic deletion variants in the GSTM1 and GSTT1 genes produce a functional enzyme (non-deletion alleles or heterozygous deletion, GSTM1-1 and GSTT1-1) or result in the complete absence of the enzyme (homozygous deletion alleles, GSTM1-null and GSTT1-null).[16] GSTM1-null and GSTT1-null variants in some studies were associated with increased susceptibility to inflammatory processes, male infertility, and increased risk of cancers or pre-malignant conditions.[15,17-21] However, these studies have yielded contradictory results. We did not find reliable data of GSTM1 and GSTT1 genes association with GERD.

Therefore, we performed an investigation of deletion (null) polymorphism of GSTM1 and GSTT1 genes' alleles, genotypes and haplotypes frequency in GERD patients with diabetes mellitus type 2 (DM2). The aim of our study was to establish the difference in null GSTM1 and GSTT1 genes polymorphisms between GERD patients with and without diabetes in Northern Bukovina (Western Ukraine).

Patients and methods

Study was performed in compliance with the Council of Europe Convention on Human Rights and Biomedicine and recommendations of the Committee on Bioethics of the Ministry of Health of Ukraine. Patients' Examination Cards and Patients' Informed Consent Forms were approved by the Biomedical Ethics Commission of Bukovina State Medical University, Ministry of Health of Ukraine (Chernivtsi, Ukraine). All enrolled patients were treated in the Gastroenterology Department, Regional Clinical Hospital (Chernivtsi, Ukraine) during January-December, 2012. Genetic bench study performed in the laboratory of Medical Biology and Genetics Department of Bukovina State Medical University. After screening (matching inclusion/exclusion criteria) 50 GERD patients were selected for further examination.

Inclusion criteria

Patients with GERD typical symptoms for 6 months (heartburn and/or acid regurgitation minimum twice weekly); atypical symptoms (epigastric pain, nausea, belching, halitosis, pseudo-angina pain); or with erosive GERD discovered during endoscopic examination (reflux esophagitis); or at the stage of GERD complications (peptic stenosis of the esophagus, digestive hemorrhage).[22-24] Patients with GERD and only with type 2 diabetes mellitus (DM2) were included.

Exclusion criteria

We excluded patients from the study treated surgically for GERD or presenting symptoms of GERD once a week or less frequently; or presenting undercurrent factors that can cause disorders like bulimia or anorexia; professionals exposure to toxic agents (acid fumes and aerosols used in industry); pregnant women or in lactation period; subjects with psychological disorders; patients with DM1.

Diagnosis of GERD

15 patients of the study and control groups were newly diagnosed patients observed at the Gastroenterology Department, Regional Hospital; 35 patients – with chronic GERD. Gastro-esophageal reflux disease was diagnosed by esophagogastroduodenoscopy and esophageal pH-metry according to Montreal Consensus.[22] All enrolled patients underwent endoscopy.

Genomic DNA was extracted from peripheral blood leukocytes using the "DNA-sorb-B" test system, with primers specific to the genes' alleles.[25] Detection of GSTM1 and GSTT1 genes deletions was performed by the multiplex polymerase chain reaction (PCR) according to the manufacturer's protocol. Allele-specific primers were used in the PCR (**Table 1**). The PCR was performed in a total volume of 25 µL containing: 200 ng of isolated DNA, 65 mM Tris-HCl pH=8.9, 0.05% Tween20; 16 mM $(NH_4)_2SO_4$, 3.5 mM $MgCl_2$), 0.8×SYBR Red, 0.2 mM of each dNTPs (dATP, dTTP, dGTP and dCTP), 0.3 µM of each primer for GSTM1 and albumin, 0.3 µM of each primer for GSTT1 and 0.5 of thermostable Taq polymerase (Applied Biosystems, USA). The amplification conditions were subjected to initial denaturation at 94 °C for 10 min; 35 cycles consisting of denaturation at 94 °C for 1 min, primer annealing at 60 °C for 30 s and DNA elongation at 72 °C for 45 s; the final DNA elongation was at 72 °C for 10 min. The multiplex PCR products (GSTM1-219 bp, GSTT1-459 bp and albumine-350 bp) were separated by horizontal electrophoresis on 3% agarose gels, containing 4 µL of ethidium-bromide and visualized by in the presence of molecular mass ladder (100-1000 bp) using a UV transilluminatior (Nyxtechnic, USA). Both GSTM1 and GSTT1 products were categorized as having either a non-null or null (homozygous deletion) genotype (**Fig. 1**).

Statistical analysis

Statistical analysis was performed using Statistica 7.0 (StatSoft Inc, USA) software. p value and odds ratio (OR), with 95% confidence interval (CI) using a chi-square test were determined for the calculated frequencies of each allele, genotype and haplotypes. Risk ratios (RR) were estimated by OR. Adjusted OR and 95% CI were estimated for the association between the severe erosive esophagitis of II-III stages, DM2 and genetic polymorphism. p values ≤0.05 were considered statistically significant.

Results

The prospective study included 50 patients with GERD: study group – 33 patients with GERD + compensated DM2, among them – 16 patients with GERD and erosive esophagitis of I-III severity stages + compensated DM2 and 17 patients with GERD, non-erosive esophagitis + compensated DM2; control group – 17 patients with GERD without DM2, among them – 7 patients with GERD and erosive esophagitis of I-III severity stages, 10 subjects – GERD and non-erosive esophagitis. Duration of GERD varied from 1 to 8 years (mean 5.69±1.03 years).

Detection of GSTM1 deletion and GSTT1 deletion was performed in 33 patients with GERD and DM2 (study group) and 17 patients with GERD and without DM2 as control group. Deletion of the GSTM1 gene was detected in 12 (36.4%) study group patients and in 6 controls (35.3%) (p>0.05), while the GSTT1 gene deletion polymorphism was detected in 5 study group patients (15.2%) and in 2 controls (11.8%) (p>0.05).

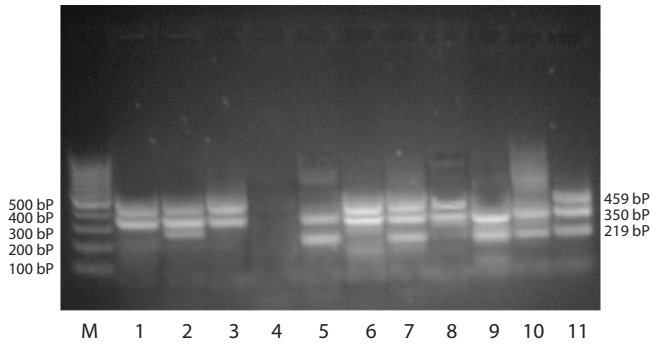

Figure 1. Electrophoregramm of human DNA PCR products amplification of glutathione-S-transferase classes T1 (*GSTT1*) and M1 (*GSTM1*) genes polymorphism. M – Marker GeneRuler™ – DNA Ladder (1000-100 bp); lines 1, 3, 6, 8 – homozygous deletion (0/0) in *GSTM1* gene (null genotype); lines 2, 7, 11 – positive (non-null) gemotype in both genes *GSTT1* and *GSTM1* (presence of functional 1 alelle); lines 5, 9, 10 – homozygous deletion (0/0) in *GSTT1* gene (null genotype); line 4 – positive PCR control.

The overall frequency of GSTM1 null genotype was 1.75 times lower in study group compared with non-null GSTM1 (c^2=4.91, p=0.027). There was no significant difference within the control group (c^2=2.94, p>0,05).

The number of study group patients with non-null GSTT1 was 5,6 times higher than with null GSTT1 (c^2=32.1, p<0.0001). Similarly, non-null GSTT1 prevailed (7.5 times) in control group (c^2=19.9, p<0.0001).

Both deletions were present only in 1 study group patient (3.0%) and was not found in control (**Table 2**).

Thus, almost half (48.0%) of patients with GERD have a mutation in the promoter area of the studied GST genes. Every third patient (36.0%) is the carrier of a mutant 0/0-genotype of GSTM1 gene in haplotype, while the combination of homozygous GSTT1 gene mutations observed 2.6 times less (14.0%). Linked mutation is absent in 52.0% of patients.

No significant differences were found in distribution of GSTM1 and GSTT1 haplotypes between both groups. Neither GSTM1 null mutation, nor GSTT1 null mutation increase the risk of GERD and DM2 incidence, independently on types and severity of esophagitis (OR=0.48-2.03, 95% CI=0.06-8.66, p>0.05).

The frequency of GERD and non-erosive esophagitis did not depend on the haplotypes and concomitant DM2, whereas non-erosive esophagitis was the most frequent pathology among the patients: 17 (34.0%) in study group and 10 (20.0%) in control. Combination of functional (1) alleles of both genes in haplotypes associated with more often presence of GERD and non-severe erosive esophagitis I stage (26.9%). The presence of GSTM1 0/0 mutant homozygote in haplotypes (GSTT1+/GSTM1–) is accompanied by an increase the number of patients with GERD, DM and erosive esophagitis II stage (23.5%) versus GSTM1+/GSTT1 0/0 carriers (16.7%, c^2=5.48, p=0.041).

No statistically significant associations between the haplotypes of GSTM1 and GSTT1 genes and GERD/DM2 presence were observed, depending on smoking. Similarly, age, gender, smoking habits, and type of esophagitis did not associate with the risk of GERD/DM2 (**Table 3**).

Presence of homozygous deletion in the promoter areas of GSTT1 and GSTM1 haplotypes did not significantly increase the risk of comorbid condition DM2 in GERD patients.

Discussion

GERD and DM2 are heterogeneous disorders, with various genetic and environmental factors like diet and changes of microbiota[26] contributing to the reflux of stomach contents causing troublesome symptoms and/or complications (erosive esophagitis, etc) and disorders in glucose/insulin homeostasis. In our study, we analyzed two different genes (GSTM1 and GSTT1) in GERD patients with and without DM2.

Deletions of GSTM1 and GSTT1 genes cause an imbalance of pro-oxidants and antioxidants in esophageal sphincter tissue, influence glucose metabolism, insulin-resistance that could play a role in the etiology of both GERD and DM2. Inter-individual variability in GST enzymatic activity can influence the increased susceptibility to DM2, especially in those with environmental determinants, pernicious habits, obesity, etc.[4,8,14,27,28]

The variability in the distribution of the null genotypes of GSTM1 and GSTT1, due to total or partial gene deletion resulting in the lack of the active enzyme, has been reported in different populations.[27-31] Kala Z et al.[32] hypothesized that polymorphisms in genes for detoxifying enzymes (GSTM1, GSTT1 and GSTP1) could influence susceptibility to reflux esophagitis (RE) and Barrett's esophagus (BE) (the most common esophageal complications of GERD). The GSTM1 and GSTT1 genes did not show any relationship with reflux disease, but the GSTP1 gene might be one of the risk factors associated with susceptibility to RE, especially to BE. Liu B et al.[33] performed case-control study (109 patients with RE, 97 patients with nonerosive reflux disease (NERD) and 97 normal controls) and proved that the subjects with GSTT1 and GSTM1 polymorphisms did not show any correlation with high risk for RE or NERD. No significant interactions were identified between the variant GSTs and cigarette smoking, or alcohol drinking and subtype of RE. In our study similarly GSTM1 and GSTT1 genes did not associated to GERD with or without DM2, regardless smoking. The association of GSTM1 and GSTT1 genetic polymorphism with GERD, erosive esophagitis and DM2 in west-Ukrainian patients was studied for the first time.

DNA damage and mutation in detoxification enzymes, including the GST, is a well-established risk factor for tobacco-related diseases. In the current study, we evaluated interaction between GSTM1/GSTT1 genotype and smoking in GERD+DM2 cases and control, it was found that smoking does not significantly associate with the risk of GERD and DM2 either in GSTM1 / GSTT1-positive or null genotype. Otherwise, Casson AG et al.[34] reported that cigarette smoking is an independent risk factor for esophageal adenocarcinoma (EADC), especially when cigarette exposure was greater than 30 pack-years (OR=6.11, 95% CI=2.2-17.32; p=0.001). The strong association between smoking and EADC was seen preferentially in patients with the active allele of either GSTM1 (OR=7.9, 95% CI=1.14-54.76; p=0.003) or GSTT1 (OR=3.2, 95% CI=1.23-8.35; p=0.004). Kim SJ et al.[35]

Table 1. Primer sequences for GSTM1 and GSTT1 genes SNPs

SNP locus	Primers	Primer sequences (5′-3′)	Size of fragments, bp
GSTM1	Forward	5′GGTCAAGGACATCATAGACGAGAA3′	219
	Reverse	5′CTCAGGAGAAACTGAAGCCAAA3′	
GSTT1	Forward	5′GCTAGTTGCTGAAGTCCTGCTTA3′	459
	Reverse	5′CTTGGCCTTCAGAATGACCT3′	
ALB	Forward	5′TGGGTGCTAGAGGTATAATCG3′	350
	Reverse	5′TTAGAGGAAGCTGGGTAAGAG3′	

ALB, Part of the albumin gene, as an internal amplification control; SNP, single-nucleotide polymorphism.

Table 2. Distribution of GSTM1 and GSTT1 genotypes in observed subjects

Combination of GSTM1 та GSTT1 genotypes	Study group, n=33 (%)	Control group, n=17 (%)	OR	95% CI	p-value
GSTM1+/GSTT1+, n=26	17 (51.5)	9 (52.9)	0.97	0.36-2.64	>0,05
GSTM1+/GSTT1 –, n=6	4 (12.1)	2 (11.8)	1.03	0.17-6.20	>0,05
GSTT1+/GSTM1–, n=17	11 (33.3)	6 (35.3)	0.94	0.30-2.99	>0,05
GSTT1–/GSTM1 – n=1	1 (3.0)	N/A	–	–	–

"+", presence of functional allele (wild type) of GSTM1, GSTT1 genes; "–", null (0/0) genotype (mutant type); n (%), number (percentage); N/A, not available..

Table 3. Association between haplotypes of GSTM1 and GSTT1 genes and GERD / DM2 present depending on age, gender and smoking status

No.	Potential risk factors		Case, n=33 (%)	Control, n=17 (%)	OR (95%CI)	p-value
1	Age, years	<60	28 (84.8)	14 (82.4)	0.83 (0.17-3.99)	>0.05
		≥60	5 (15.2)	3 (17.6)		
2	Gender	Male	15 (45.5)	6 (35.3)	1.53 (0.46-5.11)	>0.05
		Female	18 (54.5)	11 (64.7)		
3	Smoking	Yes	10 (30.3)	6 (35.3)	0.80 (0.23-2.76)	>0.05
		No	23 (69.7)	11 (64.7)		
4	Esophagitis	Erosive	16 (48.5)	7 (41.2)	1.34 (0.41-4.39)	>0.05
		Non-erosive	17 (51.5)	10 (58.8)		

OR, odds ratio; OR (95%CI), OR confidence interval.

found that smokers with GSTM1-positive genotype in cases of coronary artery disease (CAD) were at approximately 1.21-fold higher risk of CAD and it was slightly higher with GSTM1/T1-null genotype compared to non-smokers with GSTM1/T1-positive genotype.

Many studies assessed the associations between GSTM1/GSTT1 null genotypes and DM risk but reported dissimilar results in populations, races, or ethic's groups.[36-39] Zhang J et al.[28] performed meta-analysis of GSTM1/GSTT1 null genotypes associations with DM risk (11 publications, a total of 2577 cases and 4572 controls). Meta-analyses indicated that null genotypes of GSTM1/GSTT1 and dual null genotype of GSTM1/GSTT1 were associated with increased risk of DM (GSTM1: OR random-effects=1.60, 95% CI=1.10-2.34, POR=0.014; GSTT1: OR random-effects=1.47, 95% CI=1.12-1.92, POR=0.005; GSTM1-GSTT1: OR fixed-effects=1.83, 95% CI=1.30-2.59, POR=0.001). This meta-analysis suggests null genotypes of GSTM1/GSTT1 and dual null genotype of GSTM1/GSTT1 are potential biomarkers of DM. However, exact mechanism of how presence of the null genotype increases risk of DM is not clear, yet. Similarly, it is not clear how null genotype influences pathogenesis of GERD and it complications.

The GSTM1 null genotype frequencies vary from 38% to 67% in European populations, from 33% to 63% in Asians and from 22% to 35% in Africans and African-Americans.[29,40] In Brazilian urban populations, the GSTM1 null phenotype frequency varies from 46% to 49%, but in Brazilian Amerindian population – from 0 to 43%.[27,41] Significant differences in GSTT1 null allele frequencies were observed between Caucasian, Asian, African and African American populations.[42] Korean population showed higher frequency of GSTT1 null allele (45.3%) compared with the white Americans (20.4%), African Americans (21.8%), Mexican-Americans (9.7%) and Turkish populations (10.8%-28.3%).[42-44.] The GSTT1 null genotype frequencies vary 0-19.8% in European populations, 3%-39% in Asians.[30,41,42,44] The prevalence of GSTM1 and GSTT1 null allele in the present study ranges from 35.3 to 36.4% for GSTM1 and from 11.8% to 15.2% for GSTT1, which is almost similar to the frequencies reported in Caucasians.

In conclusion, our finding may be an important contribution towards the identification of the role of genetic polymorphism of GST interactions for GERD+DM2 risk. Our results suggest that GSTM1 and GSTT1 null genotype has no association with the risk of DM2 in West-Ukrainian GERD patients' regardless their smoking status. Further studies including examination of other genotypes and genes involved either in metabolic process or detoxification are anticipated to improve our ability to find genetic factors contributing to DM or/and GERD susceptibility.

Limitations of the study

The present study was limited by a number of enrolled subjects; absence of individuals without GERD; patients were not all at the same stage of GERD; GSTP1 gene polymorphisms were not evaluated.

Conflicts of interest

The authors declared no conflicts of interest.

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