Investigation The Relationship Between GSTT1, GSTM1 Gene polymorphism and Type 2 Diabetes Mellitus in men patients

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Abstract

The glutathione S-transferases (GSTs) are involved in the metabolism of many xenobiotics, including an array of environmental carcinogens, pollutants, and drugs. GSTs play an important role in cellular protection against oxidative stress. Genetic polymorphisms in these genes may lead to interindividual variation in susceptibility to various diseases such as diabetes mellitus type2. A relationship between these polymorphisms and changes in the clinical parameters of diabetic patients has also been investigated. However, the results diverge considerably among the studies, Thus, this case-control study was designed to contribute to existing knowledge, as there are no studies on this issue performed in the Iraqi population. The study consisted of 50 clinically diagnosed diabetes mellitus type2 patients and 31 healthy control men. Analyses of GST polymorphism were carried out by multiplex PCR. Our results showed GSTT1 null and for GSTM1 null compared to GSTT1 present and GSTM1 present genotypes respectively the proportion of GSTT1 null genotypes were higher in diabetic patients as compared to controls (30 % versus 6.5%). No significant difference of the frequency of GSTM1 null that observed between cases and controls (52% versus 54.8%). We conclude GSTT1 gene polymorphisms may play an important role in diabetes mellitus type 2 pathogenesis. The GSTM1-null genotype may be helpful in identifying individuals at high risk for essential hypertension in study population and the potential role of GSTM1 polymorphism as a marker of susceptibility to type 2 diabetes mellitus needs further studies in a larger number of patients. GSTT1 and GSTM1 genotypes do not have an effect on blood lipids given exposure to diabetes mellitus.

Introduction:

Diabetes Mellitus Type 2 (T2DM) is a multifactorial disease that develops through an exposure to environmental risk factors, lifestyle habits and genetic susceptibility. This heterogeneous syndrome is characterized by chronic hyperglycemia and other metabolic alterations. These mainly include dyslipidemia and hypertension that leads to a development of macro and microvascular complications. The disease pathogenesis involves a combination of β-cell insufficiency and insulin resistance. Much like other multifactorial diseases little is known about the genetics of T2DM (1).

Oxidative stress, arising as a result of an imbalance between free radicals and anti-oxidant defenses, is associated with damage to lipids, proteins and nucleic acids, which could contribute to cellular dysfunctions leading to the pathophysiology of various diseases including diabetes mellitus, atherosclerosis and cancer (2) .Tissue damage due to excessive production of reactive intermediates (reactive oxygen species (ROS), reactive nitrogen species (RNS), lipid peroxides, free radicals) has been shown to be a major part of various pathologies including atherosclerosis, diabetes, cancer, ischemia-reperfusion injury, aging, and liver injury from both alcoholic and non-alcoholic origins(3,4).

Pancreatic β-cells have emerged as a putative target of oxidative stress-induced tissue damage, and this seems to explain in part the progressive deterioration of β -cell function in type 2 diabetes mellitus (T2DM)(5).

Organisms have evolved many defense mechanisms as protection from these reactive intermediates (antioxidant). These include, but are not limited to, various enzymes such as glutathione transferases (GSTs) superoxide dismutase, Se-dependent glutathione peroxidase, catalase, glutaredoxins and peroxiredoxins (6). Beta cells are very sensitive to cytotoxic stress because they express very little of the antioxidant enzymes. Hence, beta-cell is at greater risk of oxidative damage than other tissues with higher levels of antioxidant protection (7).

GSTs are a family of detoxification enzymes catalyze the conjugation of toxic and carcinogenic electrophilic molecule with glutathione and there by protect cellular macromolecules against toxic foreign chemicals and oxidative stress by free radical scavenging. Human GST enzymes are divided into three main families: cytosolic, mitochondrial and membrane-bound microsomal(8). In humans, the GSTM1 gene is situated in the GST μ cluster, which has been localized to

chromosome one in the region (1p13.3). The cluster contains four other μ class genes in addition to GSTM1, namely GSTM2, M3, M4, and M5 (9). GSTM1 is polymorphic, three alleles have been described: GSTM1*A, GSTM1*B and GSTM1*O. The GSTM1*A and *B alleles differ only by p.K172N amino acid exchange and seem to be functionally identical (10). The GSTM1*O allele has been shown to be the result of a deletion of the entire GSTM1gene (11). Loss of GSTM enzyme function is ascribed to a homozygous deletion of this gene resulting in the GSTM1*0 allele. It has been suggested that the mutation is a result of an unequal crossing over of the M1 and M2 loci (12). The presence of the GSTM1*A allele has been associated with a decreased risk of bladder cancer with the implication that detoxification of possible bladder specific carcinogens may occur in these individuals (13).

The Theta class of GSTs consists of two different subfamilies: GSTT1 and GSTT2. Genes encoding both proteins are located on chromosome 22q11.2 and are separated by 50 kb (14). Polymorphisms exist within both genes including a null phenotype (GSTT1*0) that exhibits decreased catalytic activity and has been associated with an increased risk of cancers of the head, neck and oral cavity (15).

According to the reviewed literature, few studies have been published on the association between *GSTT1/GSTM1* polymorphism and susceptibility to diabetes, and there are large divergences among the study results. These range from significant associations by only one of the polymorphisms to diabetes, by both of them, or by neither (16). This first case-control study on the Iraqi population was designed to provide more information about the effects of the *GSTT1* and *GSTM1* polymorphisms on T2DM risk and the complications associated with this disease. We have obtained important results regarding the contribution of GST polymorphisms to T2DM.

Subjects and Methods:

The study consisted of 50 clinically diagnosed diabetes mellitus type2 patients and 31 healthy control men. Their age rang was (32-83) years, from National – Diabetes Center, Al-Mustansiriya University. The following detailed in formations were obtained: Age, weight, height, Diastolic blood pressure and Systolic blood pressure (DBP,SBP), Body Mass Index (BMI), Fasting Blood sugar FBS), Blood Urea (BU), Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), and Very Low Density Lipoprotein (VLDL).

Collection of blood Samples:

Five milliliters of blood of each patient and healthy human were obtained by vein puncture using 5 ml disposable syringes after (12-14) hours fasting. The blood sample was divided in to two aliquots :(3ml) and 2ml.The first aliquot 3ml is dispensed in a plain test tube and left for around an hour to clot at room temperature, and then separated by centrifugation at 3000 rpm for 10min to collect serum. The separated serum used for assays of lipid profile and fasting plasma glucose.

Genomic DNA extraction and genotyping:

Genomic DNA was isolated from 2 mL whole blood collected in EDTA tubes using the Wizard genomic DNA purification kit (promega, USA), All samples showed bands, which indicated the genomic DNA on the gel electrophoresis (Figure 1). PCR amplifications were performed in a total volume of 50µLcontaining 5 µL genomic DNA, 14 µL D.W., 25 µL master mix and 1 µL of each primer. as follows: GSTM1F were: 5' GAA CTC CCT GAA AAG CTAAAG C 3';GSTM1R: 5' GTT GGG CTC AAA TAT ACG GTG G3'. The GSTT1F: 5' TTC CTT ACT GGT CCT CACATC TC 3' and GSTT1R: 5' TCA CCG GAT CATGGC CAG CA 3'. The primers for albumin wereALBF: 5' GCC CTC TGC TAA CAA GTC CTA C 3'and ALBR: 5' GCC CTA AAA AGA AAA TCG CCAATC3', Albumin Primers as an internal control. Thermal cycling conditions were as follows: an initial denaturation step at 95°C for 3 min, 30 cycles at 94°C for 1min, 59°C for 1min and 72°C for 1 min, and a final extension step at 72°C for 5 min. The amplification products were size separated on 2% agarose gels and visualized by ethidium bromide staining (5%).

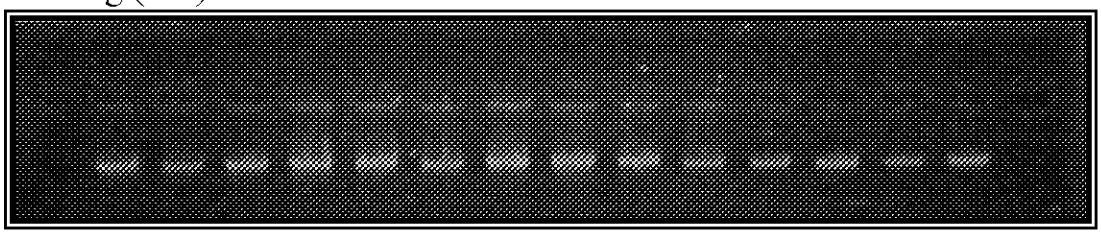

Figure (1): Agrose electrophoresis of the genomic DNA samples. Fragments were fractionated by electrophoresis on 0.8% agarose (1h/70v), 1x TB (tri-borate buffer) and visualized by ethidium bromide staining.

GSTM1 & GSTT1 genotypes were determined by the presence and absence (null) of bands of 210 bp and 480 bp, respectively, with an internal control of 260 bp. Using this genotyping assay of GSTM1 and GSTT1, the null genotypes can be clearly categorized, but the heterozygote and homozygote positive genotypes could not be differentiated (16) (Figure 2).

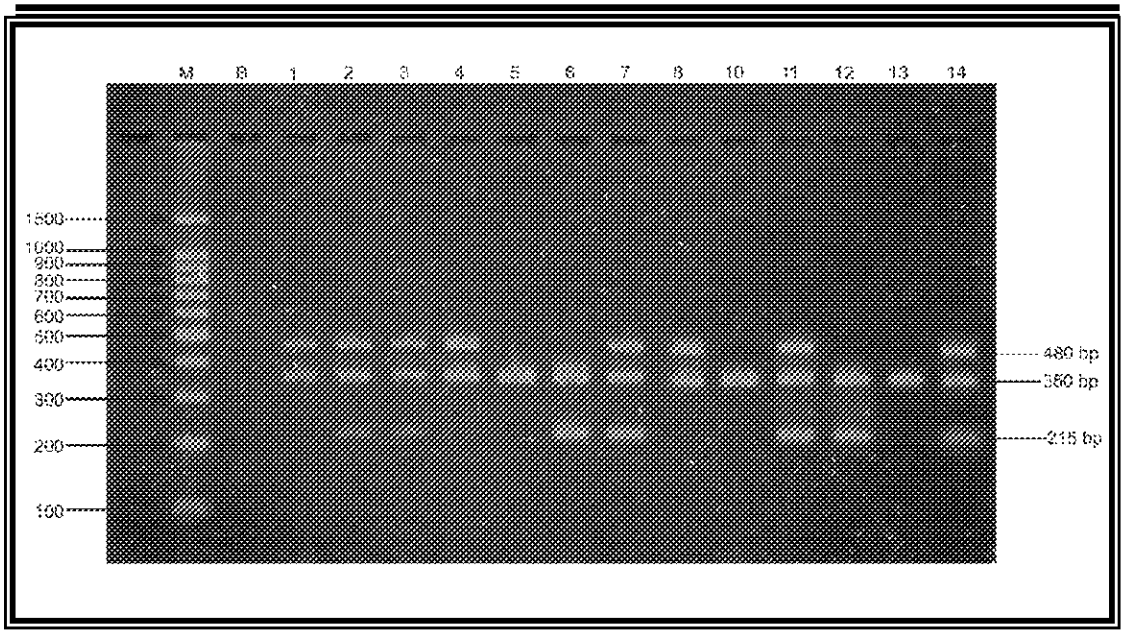

Figure (1): A representive multiplex PCR analysis of GSTs polymorphism. GSTM1 and GSTT1 genes PCR products resolved by (2%) agarose gel electrophoresis (1hr/70v).Lane M, DNA molecular weight marker. Lane B, negative controle. Lane (1-14) is samples. A 350 pb DNA fragment corresponding to the albumin gene product provides an internal positive control for each reaction and can be seen in all PCR reaction. A 215 pb is present only in those individuals containing the GSTM1 gene while a 480 pb products is present only] in those individuals containing the GSTT1 gene.

Statistical Analysis

Age of the patient and the control group were compared with student's t test. The chi-square test was applied to compare differences in clinical parameters between patients and controls. GSTT1 and GSTM1 genotypes were classified as either null (homozygous deletion) or non-deleted. P-values were two-tailed and a value of < 0.05 was considered statistically significant. All analyses were performed using SPSS v. 11.5 statistical analysis software.

Results.

Table 1 shows the distribution of the GSTM1 and GSTT1 genotypes in T2DM patients and controls. A total of 81 subjects (50 patients and 31 controls) were genotyped for the deletion polymorphism of two GST isoforms. In diabetic patients, the frequency of GSTT1-null and GSTM1-null were 30.0% and 52.0%, respectively, whereas for the control group, the frequencies of GSTT1-null and GSTM1-null were 6.5% and 54.8%, respectively.

For an analysis of the risk associated with the deletion polymorphism for GSTT1, it was found that the null genotype ($p = 0.011$) is related to an

increased predisposition for T2DM. It was also observed that there was not any association of the GSTM1 deletion with susceptibility to disease (p = 0.803) in the population studied (Table 1).

Table 1: Distribution of single and double combination of GST genotypes in the study population.

	Patients(N=50)	Controls(N=31)	p-value
GSTT1			
Null (-)	30.0%	6.5%	0.011*
Present (+)	70.0%	93.5%	
GSTM1			
Null (-)	52.0%	54.8%	0.803
Present (+)	48.0%	45.2%	
GSTT1 and GSTM1			
Both present (+/+)	28.0%	38.0%	
TT1/TM1(+/-)	42.0%	54.0%	0.078
TT1/TM1(-/+)	20.0%	6.5%	
Both null (-/-)	10.0%	0.0%	

***Significant differences between groups (P < 0.05)**.

The distribution analysis for the both GSTT1 and GSTM1 genotypes can be observed. There was a low frequency of individuals who had a double null genotype (-/-), for both case and control groups (0.0 and 10.0%, respectively). A higher prevalence of individuals with a GSTT1present/GSTM1null for both groups (42.0 and 54.0%, respectively) was also observed.

Genetic polymorphism influence on clinical parameters

For the present study the clinical parameters accompanying high risk genotypes (GSTT1-null or GSTM1-null) compared to non-risk genotypes (GSTT1-present and GSTM1-present genotypes) in diabetic patients found in (Table 2,3).

Table 2: Association between null and present genotypes of GSTT1 with clinical variables in diabetic patients.

GSTT1	present	Null	p-value
BMI	27.64±3.88	27.85±3.59	0.859
SBS	12.94±1.98	12.86±1.68	0.89
DBP	8.11 ±0.72	7.80 ±0.77	0.176
FBS	179.40 ±64.40	196.60 ±78.76	0.423
TC	178.48 ±64.20	164.60 ±27.59	0.285
TG	173.54 ±114.36	151.20 ±80.79	0.497
HDL	47.64 ±19.14	45.4 ±8.84	0.497
LDL	98.20 ±46.97	99.13 ±16.30	0.941
VLDL	31.35 ±16.84	30.13 ±16.04	0.814

***Significant differences between groups (P < 0.05)**.

Table 3: Association between null and present genotypes of GSTM1 with clinical variables in diabetic patients.

GSTM1	present	Null	p-value
BMI	26.97±3.93	28.36±3.53	0.193
SBS	12.75±1.70	13.07±2.05	0.55
DBP	7.75 ±0.60	8.26 ±0.79	0.013*
FBS	187.71±71.16	181.65 ±67.54	0.759
TC	179.25±32.88	169.76 ±48.68	0.428
TG	154.12±75.40	178.57 ±126.97	0.417
HDL	47.33±13.80	46.60 ±19.19	0.879
LDL	101.79±34.74	95.32 ±44.85	0.576
VLDL	29.70±13.58	32.20 ±19.00	0.601

***Significant differences between groups (P < 0.05)**.

According to the results for comparison the GSTM1, GSTT1 null genotypes with different clinical parameters there is no significant association was observed (*P*>0.05) (Table 2, 3). Only in cases of GSM1-null genotype, there were higher levels of diastolic blood pressure compared to the GSTM1-present genotype (P = 0.013) (Table2).

Discussion

Diabetes mellitus is one of the most common chronic diseases in nearly all countries; the number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and reduced physical activity (17). Oxidative phosphorylation during anaerobic glycolysis generates reactive oxygen species (ROS). The islet is unusually at risk for damage by pro-oxidant forces, because it expresses very low levels of antioxidant mRNA, protein, and activity. GSTs can work as endogenous antioxidants to protect cells from oxidative stress. The GSTs catalyze the conjugation of glutathione to a wide range of electrophiles and represent a protective mechanism against oxidative stress. The GST family of genes is critical in the protection of cells from ROS because they utilize as substrates a wide variety of products of oxidative stress (18).

A large number of studies have attempted to show links between the susceptibility to diseases and GST polymorphic variants (19).

Diabetic patients showed a higher frequency of the GSTT1-null genotype (30.0%) than healthy subjects (6.5%). Our study showed that the GSTT1-null genotype resulted in a statistically significant increased risk for T2DM (p = 0.011). Thus, individuals may have decreased antioxidant defenses when this isoform was deleted. Furthermore, it has been well documented that a GSTT1-present genotype can confer

protection against the development of a T2DM (20, 21). These results suggest that the GSTT1 deletion polymorphism may play a role in the pathogenesis of T2DM. On the order hand, GSTM1 polymorphism showed no significant differences in genotypic proportions between cases (null genotype of 52.0%) and control groups (54.8% of null genotype). It was also found that there was no association of GSTM1 with susceptibility to T2DM.

Despite some divergence in the literature data, GSTT1-null and GSTT1-null/GSTM1-null genotypes have consistently been considered risk factors for the development of T2DM as reported by a meta-analysis study (22). In an Egyptian study (21), the authors found significant differences between the double present genotype (+/+) and either or both null genotypes of diabetics (P= 0.002 and P= 0.009 respectively) when compared to the control subjects. They affirm these results support the notion that GSTT1 and GSTM1 cooperatively play a protective role against the development of T2DM. Furthermore, in the Indian study (23), the results implied that there was a 1.84 increased risk for T2DM with the combination of either null genotypes of GSTM1/GSTT1 (+/- or-/+).

Our results a lower frequency of individuals who had a double null genotype (-/-), for both case and control groups (0.0 and 10.0%, respectively). A higher prevalence of individuals with a GSTT1present/GSTM1null for both groups (42.0 and 54.0%, respectively), and not found significant differences between the GSTT1-present and GSTM1-present and either or both null genotypes of diabetics, albeit not statistically different from other studies. Apparently, there was no specific reason for the observed frequency, which might be attributed to a small sample size and to chance. Further investigation with larger samples needs to be conducted to better investigate these discrepancies.

Several members of the GST family exhibit selenium-independent glutathione peroxidase activity, which plays an important role in protecting cells against lipid and nucleotide hydroperoxides (18).Some investigators have observed a variety of associations between asthma, cancer and diabetic nephropathy and GST gene polymorphisms. But little is known about the effect of GST gene polymorphisms on blood lipids.

In the present study, also compared serum cholesterol, triglycerides, and high-density lipoproteins in both diabetic subjects and the control group for GSTT1and GSTM1 genotypes (null compared to present genotypes). Among individuals with GSTM1 null and GSTT1-null, the serum cholesterol, triglycerides and high-density lipoprotein were not

significantly different from GSTM1 present or GSTT1 present. Our results agree with Wang *et al.* (18). There is no significant effect of GSTT1 null and GSTM1 null on glycemic control was observed.

In this study the significant differences in diastolic blood pressure for GSTM1 was showed. These results are in agreement with a previous report by Egyptian population (21). Bessa *et al.* in (2009), who concluded that the GSTM1-null genotype may be helpful in identifying individuals at high risk for essential hypertension in the Egyptian population (24).Conversely, Delles *et al.* in (2008) did not find an association between GSTM1 gene variants and hypertension (25). This discrepancy could be due to differences in ethnic, genetic and environmental background of the population studied.

While a relationship between GSTM1 deletion polymorphism and susceptibility to disease was not verified, it was possible to observe the influence of this polymorphism on clinical parameters related to blood pressure. Therefore, the deletion of GSTM1, as well as GSTT1, can have relevance in the clinical course of diabetic patients, since those two variables, along with lipid profile, are focal points for disease monitoring to prevent T2DM complications. The mechanisms underlying the results of association obtained in this and other works still need to be investigated with further research. Although, some of our data were statistically significant, we acknowledge that the findings presented here are preliminary because of the small number of subjects and that the study requires confirmation in a separate larger cohort.

Conclusion: Our results suggest that GSTT1 gene polymorphisms may play an important role in type 2 diabetes mellitus pathogenesis. GSTT1 and GSTM1 genotypes do not have an effect on blood lipids given exposure to diabetes mellitus.

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الخلاصة

الكلوتاثيون أس- ترانسفيراز (GSTs) : هي الأنزيمات التي تشترك في عملية التمثيل الغذائي لكثير من المركبات الكيميائية التي تدخل إلى جسم الإنسان، بما في ذلك مجموعة من العناصر البيئية المسرطنة ، والملوثات ، والمخدرات .GSTs تلعب دورا مهما في حماية الخلايا ضد الأكسدة. تعدد الأشكال الجينية في هذه الجينات قد يؤدي إلى الاختلاف بين الأفراد في التعرض للأمراض المختلفة مثل مرض السكري النوع الثاني. تم التحقق من وجود علاقة بين هذه الأشكال والتغيرات في المعايير السريرية لمرضى السكري.نتيجة للاختلاف الكبير في النتائج للدراسات فقد تم تصميم هذه الدراسة لمعرفة ارتباط جينات إزالة السمية النوع الثاني لمتعدد النمط الوراثي GSTT1,GSTM1 في ظهور مرض السكري عند الرجال. كذلك هذه الدراسة من أول الدراسات حول هذا الموضوع أجريت على مرضى السكري في الشعب العراقي.

شملت الدراسة81 عينة دم [50 عينة لأشخاص مصابين بالسكري النوع الثاني و 31 عينة لأشخاص طبيعيين كمجموعة سيطرة]. أجريت تحاليل التضاعف التسلسلي المتعدد(multiplex polymerase chain reaction) للتحري عن وجود أو غياب كل من الجين الناقل للكلوتاثايون-س من نوع ميو وثيتا في جميع أفراد هذه الدراسة.

. أظهرت النتائج بأن التركيب الوراثي GSTT1null كان أعلى في مرضى السكري بالمقارنة مع مجموعة السيطرة(30 ٪ مقابل 6,5 ٪) على التوالي . لم يلاحظ أي اختلاف كبير في التركيب الوراثي GSTM1null بين مجموعة المرضى ومجموعة السيطرة (52 ٪ مقابل 54,8 ٪) . نستنتج من ذلك بأن تعدد الأشكال الجينية ل(GSTT1) قد تلعب دورا" هاما" في مرضية داء السكري النوع الثاني . النمط الجيني GSTM1-null قد تكون مفيدة في تحديد الأفراد المعرضين لمخاطر ارتفاع ضغط الدم الأساسي في مجتمع الدراسة و الدور المحتمل لمتعدد الأشكال GSTM1 كعلامة في قابلية التعرض لداء السكري من النوع الثاني يحتاج إلى مزيد من الدراسات في عدد أكبر من المرضى.