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Review Article

Role of Glutathione S Transferases Polymorphism in type 2 diabetes mellitus, with and without micro vascular complications

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ABSTRACT
Background: *Recent studies have revealed significant interethnic differences in frequencies of polymorphic GST genes and susceptibility to certain diseases in T2DM.*
Aims and Objective: *To study the original research work published over Glutathione S Transferases Polymorphism, role in type 2 diabetes mellitus with and without micro vascular complications from year 2008-2017.*
Method: *A comprehensive web search was performed on Google research scholar, pubmed and HuGENet data base using the terms GSTM1 GSTT1 T2DM micro vascular case control year 2008-2017 and meta analysis done over the association of GSTM1 and GSTT1 polymorphism in T2DM with and without micro vascular complication (diabetic retinopathy, diabetic nephropathy and diabetic neuropathy). Total 383 T2DM with micro vascular complication, 315 T2DM without micro vascular complication and 424 healthy controls were included in the study from eligible 5 published papers.*
Result: *Result of Meta analysis show that GSTM1 & GSTT1 deletion singly or together associated with micro vascular complication.*
Conclusion: *This data has some limitations; it is restricted to five small studies. There is a need to consolidate through more research in order to reduce the generalization error.*
Keywords: *GST, GSTM1, GSTT1, T2DM, Micro vascular complication, Diabetic Retinopathy, Diabetic Nephropathy and Diabetic Neuropathy, Diabetic mellitus type 2.*

Introduction

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar[(1)].

Prevalence of type 2 diabetes mellitus (T2DM) is increasing globally and has reached epidemic proportions in many countries. The number of people with diabetes has raised from 108 million in 1980 to 422 million in 2014[(2)].The global prevalence of diabetes among adults over 18 years

of age has risen from 4.7% in 1980 to 8.5% in 2014[2].

Until recently, India had more diabetics than any other country in the world, according to the International Diabetes Foundation[3], although the country has now been surpassed in the top spot by China[4]. Diabetes currently affects more than 62 million Indians, which is more than 7.1% of the adult population[5].The average age on onset is 42.5 years[3]. Nearly 1 million Indians die due to diabetes every year[3].

Prolonged exposure to chronic hyperglycemia, without proper management, can lead to various short-term and long-term secondary complications, both of macro and micro vascular nature, which represent the main cause of morbidity and mortality in diabetic patient[6]. Hyperglycemia is the major determinant of micro vascular complication in diabetes [7,8].

Over time diabetes can damage the heart, blood vessels, eyes, kidneys and nerves, and increase the risk of heart disease and stroke. Such damage can result in reduced blood flow, which – combined with nerve damage (neuropathy) in the feet – increases the chance of foot ulcers, infection and the eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. Diabetes is among the leading causes of kidney failure [9].

Hyperglycemia can trigger the variety of processes like non-enzymatic glycation of proteins, polyol pathway, and oxidative stress, activation of protein kinase C, proinflammatory cytokines, activation of nuclear factor kappa B or lack of neural growth factor [10].

Oxidative stress is one of the patho mechanisms of chronic diabetic complications, several studies have reported beneficial effects of a therapy with trace elements able to modulate red ox status or with antioxidants that can either reduce the generation of Reactive Oxygen Species (ROS), scavenge them or interfere with alterations induced by ROS. Most of the studies have been done in animal models, e.g. cardio protective effect of sodium ferulate, ROS scavenger, has been shown in streptozocin-induced diabetic rats [11].

New approach in diagnosis is establishment of gene polymorphisms of various genes encoding enzymes that play role in etiopathogenesis of chronic diabetic complications[12]. Gene polymorphisms of aldose reductase, glutathione-S-transferase M1/T1, superoxide dismutase, catalase, glutathione peroxidase, uncoupling proteins, paraoxonase or angiotensin-converting enzyme have been described to be associated with development of diabetic neuropathy, retinopathy, nephropathy or macro vascular complications. The identification of concrete gene polymorphisms in concrete patient gives base for customized or individually tailored therapy in future [10].

Different families of antioxidants have been identified in reduction of ROS production. Glutathione S-transferases (GSTs) are the most important detoxifier of a variety of electrophilic compounds, including chemotherapeutic drugs, environmental toxins, carcinogens, and DNA products generated by ROS damage to intracell-ular molecules. Thus, GSTs play a major role as a cellular antimutagen and in antioxidant defense mechanism [13].

Many of the glutathione S-transferase genes (GST genes) undergo polymorphism; therefore, there has been substantial interest in studying the associations between particular allelic variants with altered risk of a variety of diseases. Recent studies have revealed significant interethnic differences in allelic frequencies of polymorphic GST genes and susceptibility to certain diseases [14].

Aims and Objective

To study the original research work published over Glutathione S Transferases Polymorphism, role in type 2 diabetes mellitus with and without micro vascular complications from year 2008-2017.

Method

A comprehensive web search was performed on Google research scholar, pubmed and HuGENet data base using the terms GSTM1 GSTT1 T2DM microvascular case control year 2008-2017

Search selected based on

- Polymorphism GSTM1 and GSTT1
- Cases with Type 2 Diabetes mellitus with and without micro vascular complication compared with control
- Study between year 2008 – 2017

Total 138 original research publications found over glutathione s transferases polymorphism with type 2 diabetes mellitus. The search further narrows by finding with and without micro vascular complication and year of publications 2008-2017.

Five publications found as per the criteria of my search.

Total 383 T2DM with micro vascular complication, 315 T2DM without micro vascular complication and 424 healthy controls were included in the study.

Observation and Result

Meta Analysis of glutathione S-transferase gene polymorphism in various studies in different geographic locations

Reference No.	15	16	17	18	19
Author	Datta et al (2010)	Jamil et al (2016)	K. Shukri et al (2008)	Moasser et al (2014)	Stoian A et al (2015)
Region	India	India	UAE	Iran	Romania
Method	MultiPlex PCR	MultiPlexPCR	Multiplex PCR	Multiplex PCR	Multiplex PCR
Control Healthy Sample	50	50		201	98
Mean Age	51.6±9.1	56.61±9.71		51.1±9.2	60.8±4.3
Control Healthy Deletion of Genotype GSTM1	11 (23.9)	8 (16)		98 (48.8)	38 (38.7)
Control Healthy Deletion of Genotype GSTT1	07 (16.3)	14 (28)		40 (27.1)	12 (12.2)
Control Healthy Deletion of Genotype GSTM1 GSTT1	03 (8.1)				13 (13.3)
Control Healthy Presence of Genotype GSTM1 GSTT1	29 (39.2)				35 (35.7)
T2DM with Micro vascular complication	50	50	40	201	42
Mean Age	52.2±8.8	56.61±9.71	40.8±1.045	51.3±8.6	66.2±9.3
T2DM with Micro vascular complication Deletion of Genotype GSTM1	11 (23.9)	16 (32)	11 (55)	23 (16.5)	14 (33.3)
T2DM with Micro vascular complication Deletion of Genotype GSTT1	13 (30.2)	24(48)	8 (40)	50 (24.9)	2 (4.7)
T2DM with Micro vascular complication Deletion of Genotype GSTM1 GSTT1	16 (43.3)				6 (14.3)
T2DM with Micro vascular complication Presence of Genotype GSTM1 GSTT1	10 (13.5)				20 (47.1)
T2DM without Micro vascular Complication	50		20	203	42
Mean Age yrs	57.2±10.2		42.1±1.64	52.7±10	60.1±7.5
T2DM without Micro vascular Complication Deletion of Genotype GSTM1	12 (26.1)		23 (57.5)	110 (54.2)	19 (45.2)
T2DM without Micro vascular Complication Deletion of Genotype GSTT1	05 (11.6)		24 (60)	55 (27.1)	2 (4.7)
T2DM without Micro vascular Complication Deletion of Genotype GSTM1 GSTT1	09 (24.3)				5 (11.9)
T2DM without Micro vascular Complication Presence of Genotype GSTM1 GSTT1	24 (14.9)				16 (38.1)

Meta Analysis of Individual Statistics of Studies

S.No	Study	Genotype	Group	Odd Ratio	CI 95%	P value
1	Datta et al	GSTM1 Null	T2DM with Micro vascular complication compared with healthy control	2.900	0.963-8.732	0.055
		GSTT1 Null	T2DM with Micro vascular complication compared with healthy control	5.386	1.677-17.293	0.003
		GSTM1 & GSTT1 Null	T2DM with Micro vascular complication compared with healthy control	15.467	3.711-64.456	<0.001
		GSTM1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	2.200	0.731-6.620	0.157
		GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	6.240	1.756-22.177	0.003
		GSTM1 & GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	4.267	1.420-12.824	0.008
2	Jamil et al	GSTM1 Null	T2DM with Micro vascular complication compared with healthy control	0.4	0.1-1.0	0.061
		GSTT1 Null	T2DM with Micro vascular complication compared with healthy control	0.4	0.2-1.0	0.039
3	K. Shukri et al	GSTM1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	1.1	0.38-3.3	NS
		GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	2.3	0.75-6.7	NS
4	Moasser et al	GSTM1 Null	T2DM compared with healthy control	1.43	1.01-2.04	0.03
		GSTT1 Null	T2DM compared with healthy control	1.43	0.92-2.18	0.09
		GSTM1 & GSTT1 Null	T2DM compared with healthy control	1.88	1.06-3.338	0.02
		GSTM1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	1.33	0.88-2.02	< 0.05
		GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	0.89	0.566-1.42	< 0.05
5	Stoian A et al	GSTM1 Null	T2DM compared with healthy control	0.84	0.43-1.63	0.61
		GSTT1 Null	T2DM compared with healthy control	0.32	0.09-1.10	0.09
		GSTM1 & GSTT1 Null	T2DM compared with healthy control	1.82	0.32-2.08	0.67
		GSTM1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	0.58	0.22-1.53	0.27
		GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	0.80	0.10-6.32	0.95
		GSTM1 & GSTT1 Null	T2DM with Micro vascular complication compared with T2DM without micro vascular complication	0.66	0.17-2.59	0.73

Discussion

K. Shukri et al (2008) said frequencies of null GSTM1 and GSTT1 genotypes were 55% (11/20) and 40% (8/20), respectively, in non complicated diabetes mellitus group. The frequencies of null GSTM1 and GSTT1 genotype in complicated diabetes mellitus group were 57.5% (23/40) and 60% (24/40), respectively. The null GSTT1 genotype was more prevalent in the group of complicated DM with odds ratio (odds ratio, 2.3; 95% confidence interval, 0.75-6.7) when compared with non complicated DM with null GSTT1 genotypes are substantially at higher risk for developing complications.

Datta et al (2010) said on genotyping, subjects were categorized as GSTM1+/GSTT1+, GSTM1−/GSTT1+, GSTM 1+/GSTT1−, and GSTM1−/GSTT1−. Serum GST levels were lower among subjects with deletion in one/both GST genes, whereas MDA levels were found to be correspondingly raised. A negative correlation for MDA versus GST levels was observed among genotypes with one/both gene deletions. Presence of GSTM1+/GSTT1− and GSTM1−/GSTT1− was significantly higher among patients with CKD in both diabetics and non diabetics. *Datta et al* finally concluded that GSTM1 and GSTT1deletions singly or together were associated with lower GST levels and higher oxidative stress in both diabetic and non diabetic CKD. Interestingly, GSTT1 deletion appears to be associated with both diabetic and non diabetic CKD irrespective of the GSTM1 status.

Moasser et al (2014) said Increased odds ratio showed that GSTM1-null genotype had a moderately higher occurrence in T2DM patients (OR=1.43, 95% CI=1.01–2.04; *P*=0.03) than in healthy individuals. However, the frequency of

GSTT1 genotype (OR=1.41; 95% CI=0.92-2.18; *P*=0.09) was not significantly different comparing both groups. Although, regression analysis in T2DM patients show that GSTM1 and GSTT1 genotypes are not associated with T2DM retinopathy development in the Southern Iranian population.

Stoian A et al (2015) data suggest that *GSTP1* gene polymorphisms may contribute to the development of T2DM in Romanian population. *GSTM1*, *GSTT1*, and *GSTP1* gene polymorphisms are not associated with susceptibility of developing diabetic neuropathy in T2DM patients. *Jamil et al (2016)* found that the frequency of null polymorphisms in GSTM1 and GSTT1 were higher in patients (32% and 48% respectively) when compared to controls (16% and 28% respectively). Overall, GSTT1 null polymorphism was significantly associated with diabetes when compared to controls (p=0.039). Interestingly, a large percentage of the female patients were dyslipidemic (64.86%). This indicates that patients with null polymorphisms in GSTM1 and GSTT1 may have adverse patho physiological effects which could contribute to Diabetic Nephropathy and Diabetic Retinopathy complications in T2DM.

Conclusion

- GSTM1 & GSTT1 deletion singly or together positively correlated with oxidative stress.
- GSTM1 & GSTT1 deletion singly or together negatively correlated with GST level.
- GSTM1 & GSTT1 deletion singly or together associated with diabetic retino-pathy, diabetic nephropathy and diabetic neuropathy
- GSTT1 deletion is at higher risk of developing micro vascular complication.
- Some geographical location has been found where GSTM1 and GSTT1 are not related with micro vascular complication.
- This data has some limitations; it is restricted to five small studies. There is a need to consolidate through more research in order to reduce the generalization error. Therefore, further larger studies considering the gene-gene and gene-environment interactions could be required to provide a very precise evidence for the association of *GST* polymorphism and micro vascular complication.

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