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AN ELABORATE REVIEW ON GST GENE POLYMORPHISM AND DIABETES MELLITUS

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Abstract: Type 2 diabetes (T2D) is a multifactorial disease affecting mostly adults older than 40 years. The aim of the study was to examine *GST* gene polymorphism influence on the risk of T2D, especially in young adults. Oxidative stress may be the risk factor for development of type 2 diabetes .oxidative stress is the imbalance between the antioxidant and free radicals which is associated with the damage to lipids, protein, and nucleic acid which leads to cause various disease like diabetes mellitus, cancer etc. In conclusion, the results suggest that GST polymorphism may be one of the risk factors for developing T2D at a younger age than the T2D population average.

1. INTRODUCTION

Diabetes has become an epidemic in 21th century and leads to a major public health problem[(Sharma et al., 2016). It is group of metabolic disorders which is characterized by the high blood sugar level in which body is unable to produce or respond to the hormone insulin which result in the abnormal metabolism of carbohydrates and glucose level in blood factor include age, gender, genetic or environmental factors may play important role in occurrence of type 2 diabetes mellitus[(Etemad et al., 2016).The International Diabetes Federation (IDF) has estimated that number of people with diabetes will increase from 31.7 million in 2000 to 79.4 million in 2030[(Sharma et al., 2016)[(Road & Pradesh, 2014).

Oxidative stress may be the risk factor for development of type 2 diabetes .oxidative stress is the imbalance between the antioxidant and free radicals which is associated with the damage to lipids, protein, and nucleic acid which leads to cause various disease like diabetes mellitus, cancer etc.[(Wang et al., 2006). Insulin resistance and obesity may be the risk factor for type 2 diabetes mellitus[(Etemad et al., 2016). Insulin is needed to move glucose into the cells. Beta cells have higher risk of oxidative damage than other tissue due to because they express very little amount of antioxidant enzyme[(Wang et al., 2006). So, oxidative stress is contribute to the destruction of insulin producing beta-cells.Glutathione s-transfereesare the major defense system against the oxidative stress. Glutathione s-transferees are the family of phase 2 is enzyme that function similar to many different xenobiotic in mammals and to protect the cellular macromolecule(Zaki et al., 2015).Glutathione s-transferees is the major cellular antioxidant that detoxifies the reactive oxygen species (ROS) or reduces peroxide through glutathione s-transferees conjugation[(Road & Pradesh, 2014). Glutathione s-transferees play important role in antioxidant defense mechanism.Three families of glutathione s-transferees have been found: the cytosolic glutathione s-transferees family, the mitochondrial glutathione

s-transferees family and microsomal glutathione family. These enzyme catalyzed the conjugation of reduce glutathione (GSH) of exogenous and endogenous compound. So the conjugation with glutathione is increase the solubility of the compound(Drobná et al., 2013). The cytosolic glutathione s-transferees family is mainly found in the cytoplasm but it is also present in the nucleus and mitochondria where they may play important role in defense against chemicals(Sharma et al., 2016). So the cytosolic and soluble glutathione is involve in the metabolism of foreign chemicals like environmental pollutants etc.[(Etemad et al., 2016). So these enzymes neutralize the exogenous and endogenous compound via conjugation with glutathione (GSH).In human at least 8 family have been found named Mu (M), kappa (K), alpha (A), pi (P), omega (o), theta (T) ,zeta (Z), and sigma (S) which are encoded by glutathione s- transferees M (GSTM), glutathione s-transferees K (GSTK) , glutathione s-transferees A (GSTA) , glutathione s-transferees P (GSTP) , glutathione s-transferees O (GSTO) , glutathione s-transferees T (GSTT) , glutathione s-transferees Z (GSTZ) , glutathione s-transferees S (GSTS) gene respectively.(Zaki et al., 2015)[(International et al., 2011). Each gene isconsisting of more than one enzyme. among are candidate gene , particularly glutathione s-transferees P1 (GSTP1) , glutathione s-transferees M1 (GSTM1) , glutathione s-transferees T1 (GSTT1) were widely studied and discussed in connection with susceptibility to various diseases (International et al., 2011). Polymorphism in glutathione s-transferees arises from the nucleotide alternation that changes the codon and generates null genotype.Glutathione s-transferees T1 (GST T1), and glutathione s-transferees M1 (GST M1) null genotype are polymorphic in human due to the lack of enzymatic activity. so the glutathione s-transferees M1 null genotype are the risk factor for type 2 diabetes mellitus [(Amer et al., 2011)]. In this study, we investigate the polymorphism of glutathione s-transfereesM1 (GSTM1), glutathione s-transferees T1 (GSTT1), glutathione s-transferees P1 (GSTP1) gene occur in type 2 diabetes mellitus.

2. DIABETES MELLITUS

Diabetes mellitus is a group of diseases which is characterized by the high levels of blood glucose which result in defect in insulin production, insulin action, or may be both. According to the Indian council of medical research (ICMR), a national diabetic study, India currently has 63 million people with diabetes and it will be increased over 100 million by 2030. India represents the world's second largest diabetic population after china and most of the people with diabetes (> 90 %) have type 2 diabetes mellitus.

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There are four major clinical classes of diabetes mellitus:

TYPE 1 DIABETES

It referred to as insulin – dependent diabetes mellitus. Type 1 diabetes begins early in life and symptoms quickly become rigid. It is a chronic disease in which cells in the pancreas that makeinsulin are destroyed and body is unable to make insulin. Type 1 diabetes requires both insulin therapy and careful, lifelong control of the balance between dietary intake and insulin dose. Symptoms of type 1 diabetes include excessive thirst, dry mouth, frequent urination, fatigue, blurry vision, increased hunger, rapid breathing, belly pain, fruity smell in our breath.

TYPE 2 DIABETES MELLITUS

It referred to non – insulin dependent diabetes mellitus and also called insulin – resistant diabetes. In this it is slow to develop and the symptoms are milder and unrecognized at first. It is a group of diseases in which activity of insulin is disordered which means insulin is produced, but some feature of the insulin is defective. It is a chronic disease in which it is characterized by the high levels of sugar in blood. Type 2 diabetes is also called adult – onset diabetes because it starts almost always in middle and late-adulthood more and more children and teen is developing this condition. Type 2 diabetes is much more common than type 1 diabetes, and is really a different disease it shares with type 1 diabetes high blood sugar level, and the complications of high blood sugar.Type 2 diabetes mellitus remains related with mortality and morbidity. Over a time chronic complications have been improved [(Eizirik et al., 2020)]. In Type 2 diabetes, larger number of drug classes is used to treat these diseases. for example metformin , insulin plus metformin which improve the beta-cell function[(Eizirik et al., 2020)].

Insulin resistance: It refers to decreased tissue sensitivity to insulin. Normally, insulin binds to the special receptors on cell surfaces and initiates a series of reactions which are involved in the glucose metabolism.In type 2 diabetes, these intracellular reactions are reduced, so delivery of insulin is less effective at stimulating glucose uptake by the tissue and at regulating glucose release by the liver. The exact mechanism that leads to insulin resistance and impaired insulin secretion in type 2 diabetes are unknown, although genetic factor are thought to play a role.Majority of individualswith type 2 diabetes mellitus have insulin resistance which is present in the early stage of impaired glucose tolerance[(Goldstein, n.d.)].Action of insulin sensitivity in tissues is reduced due to the insulin resistance[(Goldstein, n.d.)].Insulin resistance affects the metabolic process and tissue function example- hyperinsulinemia encourages the sympathetic nervous system, which may lead to hypertension[(Goldstein, n.d.)].

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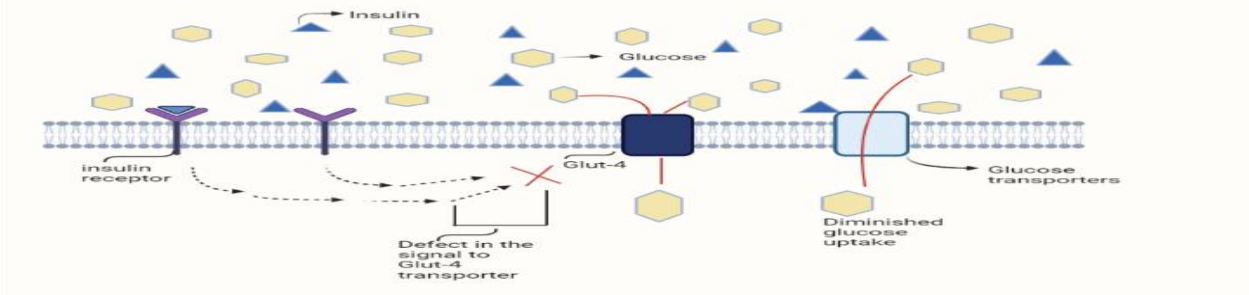

Figure 1: Insulin resistance in diabetes mellitus type 2

Impaired pancreatic beta-cell function: Insulin secretion and sensitivity are interrelated.In type 2 diabetes mellitus, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance.Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion.The response to other non-glucose such as arginine is preserved.The insulin secretory defect progresses to a state of grossly inadequate insulin secretion.The reason for the decline in insulin secretory capacity in type 2 diabetes mellitus is unclear.The assumption is that a second genetic defect ---superimposed on insulin resistance---leads to beta cell failure.Ultimately, beta cell failure may ensue.Liver and muscles identified a great supporter of systemic insulin resistance[(Zaccardi et al., 2016)].

TYPE 3 DIABETES: secondary diabetes, due to pancreatectomy, drug and other.

TYPE 4 DIABETES: (1) gestational diabetes occurs around= 20-24 week of pregnancy. (2) Placental hormone cause = insulin resistance.

GESTATIONAL D IABETES: Gestational diabetes is a condition in which high blood sugar level accumulates during the pregnancy. It affects up to 10 % of women who are pregnant in the U.S each year. There are two classes of gestational diabetes. Women with class A1 can manage it through diet and exercise. Those who have class A2 need to take insulin or other medications. Symptoms of gestational diabetes are: excessive hunger, excessive thirst, fatigue, fetal macrodome, frequent urination etc.

Factors stimulating insulin secretion:Glucose: the effect is more pre dominant when glucose is administered orally. Arise in blood glucose level is a signal for insulin secretion, Amino acid, gastrointestinal hormones: gastrointestinal hormones (secretin, gastrin)enhance the secretion of insulin.Factors inhibiting insulin secretion: Epinephrine is the most potent inhibitor of insulin release. In emergency situation like stress, extreme exercise and trauma, the nervous system stimulates adrenal medulla to release epinephrine.Epinephrine suppresses insulin release and promotes energy metabolism by mobilizing energy-yielding compounds-glucose from liver and fatty acid from adipose tissue

ACTION OF INSULIN: Insulin stimulates the transport across cell membrane by ATP dependent transporter GLUT4 to the plasma membrane.The second messenger and certain tyros in phosphorylated guanine nucleotide exchange protein play crucial role in insulin sensitive translocation of GLUT4 from cytosol to the plasma membrane, especially in the skeletal muscles and adipose tissue.Over a period of time insulin also promotes expression of

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the genes directing synthesis of GLUT4.Genes for a large number of enzyme and carrier are regulated by insulin through ras/raf and MAP kinase as well as through the phosphorylation cascade.Any type of diabetes individual are unable to take glucose from the blood in which insulin activate the movement of GLUT4 glucose transporters to the plasma membrane in muscle and adipose tissue.With glucose inaccessible, fatty acid become the principal fuel which leads to the other feature of metabolic change in diabetes and excessive but incomplete oxidation of fatty acid in the liver.The acetyl-coA is produced by beta-oxidation which cannot be completely oxidized by the citric acid cycle because of high NADH/NAD+ ratio which is produced by the beta-oxidation.Acetyl coA leads to the overproduction of ketonebodies and acetoacetate which cannot be used by the extra hepatic tissues as they are made in the liver. Diabetes individual blood also containsacetone, which results from the decarboxylation of acetoacetate. The overproduction of ketone bodies is called ketosis which results in increased concentration of ketone bodies in blood (ketonemia) and urine (ketoneuria).

Glutathione S-Transferees enzyme

Glutathione S-Transferees are the phase 2 is enzyme that are include in cellular detoxification of xenobiotic and end biotic compounds [(Lohning & Salinas, 2016)] . Detoxified substances include peroxidation products,different type of chemotherapeutics, prostaglandins and larger number of substances which belongs to the environmental carcinogens such as heterocyclic aromatic amine. glutathione s-transferees have 26 KDa molecular mass and it is non-allosteric enzyme [(Lohning & Salinas, 2016)] . it is globular demerit protein with one active site per monomer [(Lohning & Salinas, 2016)] . the polypeptide chain of each monomer is differentiated into two domain i.e. domain 1 and domain 2 which consist of 8-10% of beta strands and 48 –59 % of alpha helix [(Lohning & Salinas, 2016)] . In domain 1, single subunit of glutathione s-transferees consist of N-terminal alpha/beta domain which provide binding site with GSH (G-site). N-terminal is thioredoxin like domain which consist of 4 stranded beta sheet with 3 strand which is antiparallel to one another [(Lohning & Salinas, 2016)(Wu & Dong, 2012)] .

In domain 2 , contain 80 residue to the C-terminal domain which has an alpha –helical structure forming H-Site (hydrophobic site)which is binding with the electrophilic substrate [(Lohning & Salinas, 2016)(Wu & Dong, 2012)]. GSH Binding Site (G-Site): GSH cofactor bind to the glutathione s-transferees enzyme and it is highly conserved. GSH bind at the one end of the beta-sheets with gamma-glutamyl which point toward the protein core and mainly by the interaction of hydrogen bonding with beta3beta4alpha3 [(Wu & Dong, 2012)] .

Substrate –Binding Site (H-Site): H-Site is adjacent to the G-site for GSH binding and it include three region, the loop is present between the first beta -strand and alpha4 helix, alpha1 helix and the C-terminal. As seen after sequence alignment, these regions are very volatile which contribute to different physiochemical features for binding site. So, H-site of alpha class is smaller than the mu-class enzyme. H-site is hydrophobic in alpha and mu-class enzyme whereas H-site is half hydrophobic and half hydrophilic in pi-class enzyme [(Wu & Dong, 2012)].

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3. FUNCTION

I. Catalytic activity of glutathione s-transferees: Conjugation of different structure by product of xenobiotic and oxidative stress which is catalyzed by the glutathione s-transferees, and a non-protein thiol synthesis by de novo in mammalian cell. these interaction remove the toxic substances from the cell and protect the cellular component like protein [(Chatterjee & Gupta, 2018)] .

II. Binding of non-substrate ligand by glutathione s-transferees: glutathione s-transferees include large range of activities from carcinogen detoxification to an intracellular transport of large number of substance by the non – enzymatic ligand binding. the ligand are lipophilic in nature which includes steroid hormone , bile acid (Chatterjee & Gupta, 2018)] .

III. Glutathione s-transferees role in protein-protein interaction : glutathione s-transferees act as a modulator in several signaling kinase particularly in glutathione s-transfers P1 (GSTP1) , which include C-Jun N-terminal Kinase (JNK) , protein kinase C (PK) , and epidermal growth factor receptor (EGFR) which change their efficiency within the cellular component[(Chatterjee & Gupta, 2018)] .Cytosolic GSH and microsomal GSH transferees both are involved in the metabolism of xenobiotic . The cytosolic enzyme isderived from the superfamily of genes that encode six individual classes of enzymes. In this five are known to be represented in vertebrates. Three membrane-bound glutathione s-transferees are known which are involved in xenobiotic metabolism.

Glutathione S-Transferees polymorphism

Polymorphism in glutathione s-transfereesaffects the ability of individual to press the oxidative stress and inflammation. glutathione s-transferees gene polymorphism affects the function of enzyme which is encoded by the gene through the changes in the level of gene expression and activity of protein[(Klusek et al., n.d.)] .Polymorphism is found within each class of glutathione s-transferees. The M and T class of glutathione s-transferees have null phenotype (Glutathione s-transferees GST M, GST T) which do not express active protein. In Caucasian population around 40-60% of the population have glutathione s-transferees (GST M1) allel is found which is associated with increasing risk of lungs , gastric cancer [(Nissar et al., 2017)] . Three different type of allel are found in the same locus of chromosome which include the gene deletion (glutathione s-transferees GST M1) and the other two mutation (glutathione s-transferees GST M1a and glutathione s-transferees GST M1b) which is different by C to G codon at nucleotide position. Human glutathione s-transfereesgene mapped to chromosome 22q11.2 and has 8.1kb in length.for glutathione s-transferees (GST T1) , two different allel are found one functional allel for glutathione s-transferees(GST M1)or glutathione s-transferees (GST T1) are grouped together into the positive conjugate type which are called glutathione s-transferees M1 (GSTM1) positive and glutathione s-transferees T1 (GSTT1) positive. Deleted genotype which is the inactive form of enzyme i.e. glutathione s-transferees M1-null and glutathione s-transferees T1-null. Glutathione s-

transferees P1 single nucleotide polymorphism (SNP) present on the exon 5 which is characterized by the guanine replaced by adenine at the 313 position of nucleotide gene[(Zaki et al., 2015)] .

4. ASSOCIATION OF GLUTATHIONE S-TRANSFEREES WITH DIABETES

Many studies are available about the polymorphism of glutathione s-transferees gene which is the risk factor for developing diabetes mellitus [(Klusek et al., n.d.)]. Now a,day's most common form of diabetes is type 2 diabetes mellitus. Type 2 diabetes make up about 90% cases of diabetes and rest of the 10% due to primarily type 1 diabetes. Meta-analysis or association of glutathione s-transferees with diabetes has been conducted for various population in recent years [(Gravel et al., 2018)]. Moyassar Ahmad Zaki [(Ahmad et al., 2015)] Egyptian population, 54 subject were taken which were associated with the type 2 diabetes and 51 were taken which were healthy control. Out of 54 diabetic subjects, 27 were suffering from vascular complication. Genotyping of glutathione s-transferees T1, glutathione s-transferees M1 was performed by multiplex polymerase chain reaction and genotyping of glutathione s-transferees P1 by restriction fragment length polymorphism. No significant difference was found between the diabetic patients and healthy controls regarding glutathione s-transferees M1 and glutathione s-transferees T1 null genotype frequency (p= 0.631 and p= 0.832). the only difference noted in the glutathione s-transferees P1 SNP was that the frequency of heterozygous in the A313G glutathione s-transferees P1 polymorphism diabetic patients with or without vascular complication was significantly higher as compared to the healthy controls (p= 0.023) . so, both the null genotype of glutathione s-transferees T1, glutathione s-transferees M1 were not associated with the increasing risk of type 2 diabetes mellitus. Raza st [(Road & Pradesh, 2014)] northern Indian population, total 198 subjects were taken out of 198 individual (101 subjects were associated with the type 2 diabetes and 97 were healthy control). Genotyping of glutathione s-transferees T1 and glutathione s-transferees M1 was performed by multiplex polymerase chain reaction. They observed significant association of glutathione s-transferees M1 positive (p= 0.046) and glutathione s-transferees M1 null (p= 0.046) genotype with type 2 diabetes. So, glutathione s-transfereesM1 gene polymorphism is associated with the increasing risk of type 2 diabetes mellitus.Elham Moasser [(Moasser & Reza, 2012)] southern of Iran, total of 340 individual were taken out of these 171 were suffering from diabetes patients and 169 were normal healthy control. Genotyping of glutathione s-transferees T1, glutathione s-transferees M1 were performed by the polymerase chain reaction and genotyping of glutathione s-transferees P1 were performed by the restriction fragment length polymorphism. Nuvit Gonul [(Gönül et al., 2012) Turkish population, Turkish population, here 254 patients were included and out of these 127 patients were diabetic and 127 individual was healthy control. Genotyping of glutathione s-transferees T1 and glutathione s-transferees M1 was performed by polymerase chain reaction and genotyping of glutathione s-transferees P1 were performed by restriction

fragment length polymorphism. Denise S. Pinheiro [(Risk et al., 2013)] total 267 individual were taken in this study out of these 120 individual were suffering from diabetes and 147 individual were healthy control. Genotyping of glutathione s-transferees M1 and glutathione s-transfuse T1 were performed by real time polymerase chain reaction.

5. CONCLUSION

In human the metabolism of most of drugs and xenobiotic are done by glutathione s-transferees gene. Glutathione s-transferees enzyme plays a vital role in detoxification of xenobiotic and several endogenous compounds. These endogenous compound include neurotransmitter, cholesterol, estradiol, eicosanoids etc. it also helps in metabolism of carcinogen and drugs that induce cancer growth. Glutathione s-transferees is the family of is enzyme which are distributed in the both prokaryotes and eukaryotes [(Allocati, 2018)]. Many case control studies in which glutathione s-transferees M1 and glutathione s-transferees T1 null genotype have increased risk of association with diseases (Road & Pradesh, 2014)]. In south India, Ramprasath et. al in their study on south Indian type 2 diabetes mellitus patients observed significant association between type 2 diabetes mellitus and both null genotype of glutathione s-transferees M1 and glutathione s-transferees T1 [(Ramprasath et al., 2011)]. In one study, when we compare the Chinese population and Brazilian population, glutathione s-transferees T1 gene polymorphism is significantly associated with the development of type 2 diabetes mellitus. Glutathione s-transferees T1 present genotype is associated with the 0.49 fold which decreases risk of development of type 2 diabetes mellitus as compared to glutathione s-transferees M1 null genotype. [(Risk et al., 2013)]. In addition, other studies showed that only glutathione s-transferees M1 null genotype may play important role in pathogenesis of type 2 diabetes mellitus. In accordance, an northern Indian population study reported a significant association of glutathione s-transferees M1 null genotype with type 2 diabetes mellitus and no association was found with the glutathione s-transferees(Road & Pradesh, 2014)]. In the population of Iran, glutathione s-transferees M1 null genotype odd ratio was found to be slightly higher in type 2 diabetes mellitus as compared to healthy controls. So in this study glutathione s-transferees M1 null genotype is significantly associated with the type 2 diabetes mellitus [(Moasser et al., n.d.)]. In the Egyptian population study, the author found a significant difference between the present genotype (+ / +) and both null genotype of diabetes when in comparison to the healthy controls. So the combination of heterozygous glutathione s-transferees P1 and null genotype of glutathione s-transferees M1 is significantly higher and contribute to increases in risk of type 2 diabetes mellitus [(Zaki et al., 2015)].In conclusion there was significantly decrease of glutathione s-transferees gene function which leads to increased risk of diabetes mellitus.

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Table 1: Association of GST polymorphism with diabetes in various populations

SR. NO	POPULATION	ASSOCIATION WITH DIABETES	GENE			REFERENCE
			GSTT1	GSTM1	GSTP1	
1.	China	GST T1 gene may be the risk factor for diabetes mellitus.	✓			(Wang et al., 2006)
2.	Turkish	GST M1 gene polymorphism may increases the risk of development of type 2 diabetes mellitus.		✓		(Yalin et al., 2007)
3.	Southern of Iran	GST M1 gene polymorphism is the risk factor for Type 2 diabetes mellitus.		✓		(Moasser & Reza, 2012)
4.	Turkish population	GST M1 gene polymorphism is associated with the increasing risk of type 2 diabetes mellitus.		✓		(Gönül et al., 2012)
5.	Iranian population	GST M1 null genotype is the factor for development of diabetes.		✓		(Moasser et al., n.d.)
6.	Brazilian population	GST T1 polymorphism may be the risk factor for diabetes.	✓			(Risk et al., 2013)
7.	Chinese population	GST T1 genotype was associated with increasing risk of diabetes mellitus.	✓			(Geng et al., n.d.)
8.	Northern Indian	GST M1 gene polymorphism is associated with the increasing risk of type 2 diabetes mellitus.		✓		(Road & Pradesh, 2014)
9.	Egyptian	Combination of heterozygous GST P1 and GST M1 genotype is the risk factor for diabetes mellitus.			✓	(Zaki et al., 2015)

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