

Review

The role of glutathione transferase polymorphisms in the development of diabetic nephropathy

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Primljen – Received: 23/09/2021
Prihvaćen – Accepted: 10/12/2021

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Summary

Genetic and environmental factors play an important role in the development of type 2 diabetes mellitus (DM2) and its complications. Diabetic nephropathy (DN) is one of the most common microangiopathic chronic complications of diabetes.

Oxidative stress occurs under condition of increased production of free radicals and/or decreased activity of antioxidant defense mechanisms and it is an important link in the complex mechanism of diabetic vascular changes. Glutathione transferases (GST) are enzymes involved in xenobiotic metabolism and they are part of complex antioxidant defense mechanisms. Numerous studies have found an association of GST gene polymorphism to a predisposition to various diseases, including diabetes and diabetic nephropathy.

Our and other authors' results suggest that genetic variations in enzymes involved in free radical metabolism are associated with the development of end-stage kidney disease in patients with diabetes, which could become the basis for the development of preventive and early therapeutic strategies in high risk people.

Key words: diabetes, diabetic nephropathy, glutathione transferase polymorphism

Introduction

Diabetes (DM) is one of the biggest public health problems today. The number of people suffering from DM is constantly increasing significantly, as lifestyle changes lead to a decrease in physical activity and an increase in obesity. According to estimates by the World Health Organization (WHO, 2006), high blood glucose is the third most important risk factor for premature death, after high blood pressure and cigarette smoking. Also, DM is among the 10 leading causes of death, and with three other non-communicable diseases (cardiovascular disease, malignancies and respiratory diseases) it is responsible for more than 80% of early deaths from

non-communicable diseases. It should be noted that 30% to 80% of people with diabetes still live with undiagnosed disease [1].

According to the data from the Renal Register for Bosnia and Herzegovina, until 31 December 2017, diabetes mellitus is one of the leading causes of chronic renal failure, immediately right after glomerulonephritis. The largest number of patients with diabetic nephropathy, according to the mentioned data, were patients aged 45 to 64, and slightly less patients aged 65 to 74. Also, a larger number of patients with diabetic nephropathy had type 2 diabetes mellitus [2].

Diabetes mellitus is defined as a complex metabolic disorder characterized by chronic hyperglycemia, with a disorder in the metabolism of carbohydrates, fats and proteins. The heart of diabetes is a reduced effect of insulin on target cells, which occurs due to reduced hormone secretion and/or inadequate tissue response to insulin (insensitivity of target cells to its action), and often both disorders exist in one patient. Also, it is not clear which of the abnormality is the primary cause of hyperglycemia. Type 2 diabetes is often a manifestation of a broader disorder that includes metabolic syndrome (a set of risk factors for cardiovascular disease accompanied by glucose intolerance, hyperinsulinemia, dyslipidemia, hypertension, visceral obesity, hypercoagulability/thrombophilia and microalbuminuria). The risk of complications of DM appears long before the onset of clinical signs of diabetes (when there is impaired glucose tolerance and impaired glycemic control). Obesity is one of the most important risk factors for development of type 2 diabetes, and contributes to the risk of cardiovascular disease and mortality in general [3,4,5,6].

Diabetes is a highly heterogeneous and multifactorial, polygenic disease in which many common gene variants, mostly with little effect, contribute to the overall risk of developing the disease. The risk of developing type 2 diabetes during life is 40% if one

parent had this disease, and even higher if the mother had it. Over 130 variants of the type 2 DM-related gene have been identified, however, these variants explain less than 15% of its heritability. Genetic polymorphism is the appearance of two or more discontinuous genotypes or alleles in a population that determine the diversity of individuals in it. The gene that determines an individual's susceptibility to a certain disease is called a sensitive gene and its analysis can help in taking certain preventive actions, in efforts to establish the concept of personalized medicine based on insight into the nature of individual phenotypic differences. By knowing the sensitive gene in some individuals, they may be advised to reduce exposure to certain risk factors, in order to reduce the incidence of the disease. The risk of developing diabetic nephropathy is increased several times by inheriting risk alleles at susceptibility loci of various genes like ACE, IL, TNF- α , COL4A1, eNOS, SOD2, APOE, GLUT, etc [5,6].

Chronic hyperglycemia in diabetes is associated with long-term damage and dysfunction of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Glycoregulation has the greatest importance in the control of diabetes and the development of microvascular and macrovascular complications of the disease. Chronic hyperglycemia also leads to the development of specific microvascular changes in the retina, renal glomerulus and peripheral nerves, so diabetes is the leading cause of vision loss, terminal renal failure, and neuropathy. Many different mechanisms result in progressive loss of mass and function of β -cells, which is clinically manifested as hyperglycemia and DM (from autoimmune destruction of pancreatic β -cells with consequent insulin deficiency which is usually seen in DM type I, to resistance of target tissues to insulin action, which is usually seen in DM type II) [7–9].

Once hyperglycemia occurs, patients with diabetes have an increased risk of developing a

number of complications, which reduce quality of life and increase health costs. These complications are characterized by a fairly individual rate of development, and we can metaphorically say that DM would not be a disease if there were no complications [10–14].

Diabetic nephropathy

Diabetic nephropathy (DN) causes progressive decline in renal function and is considered a major cause of end-stage renal disease in people with diabetes worldwide. Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus, characterized by the presence of persistent proteinuria (> 300 mg / day) with concomitant retinopathy but without clinical or laboratory evidence for other kidney or urinary tract diseases. It develops in about a third of patients with type 1 and type 2 diabetes mellitus. Studies have shown that genetic predisposition contributes to the development of diabetic nephropathy. The main potentially modifying factors that contribute to the individual's onset and progression of diabetic nephropathy are persistent hyperglycemia and hypertension. Diabetic nephropathy will not develop if there is no hyperglycemia regardless of genetic predisposition and other present risk factors [15–19].

Microalbuminuria has been shown to be a predictor of early mortality in patients with type 2 diabetes and is a risk factor for cardiovascular disease and kidney disease in people with the disease, but also in those who do not have diabetes [15–17].

Complications such as peripheral autonomic neuropathy are commonly seen in patients with diabetic nephropathy and are associated with increased morbidity and mortality [7,9,11].

Prospective studies in patients with diabetes have shown that diabetic retinopathy is a predictor of later development of nephropathy,

and in clinical practice, the diagnosis of diabetic retinopathy (DR) indicates possible diabetic nephropathy (DN) [7,9,11].

Increased production of reactive oxygen species (oxygen free radical) and reduced efficiency of the antioxidant protection lead to oxidative stress or oxidative modifications of molecules in our body. Numerous studies have shown that oxidative stress is an important component in the development of vascular damage in patients with type 2 diabetes and that hyperglycemia can be a link between diabetes mellitus and oxidative stress. Occurrence of oxidative stress, i.e. hyperproduction of superoxide anion in the mitochondrial transport chain, with reduced endogenous antioxidant protection, seems to be a link between pathological processes induced by hyperglycemia [20].

Oxidative stress, which occurs when the concentration of reactive oxygen species (ROS) exceeds the capacity of antioxidant protection of the organism, as well as the decrease of antioxidant protection of the organism have been shown to be significant events in the formation of DN. Hyperglycemia induces mitochondrial hyperproduction of superoxide anions and can activate various cell damage pathways. The superoxide ion is the initial oxygen free radical, formed mostly in the mitochondria, which can be converted into other more reactive oxygen species and which can damage the cell in a number of ways. Increasing the concentration of superoxide ions partially inhibits the activity of glycolytic enzyme GAPDH (glyceraldehyde 3 - phosphate dehydrogenase), which leads to an increase in the concentration of all compounds formed in glycolysis before the site where this enzyme acts. The conversion of dihydroxyacetone phosphate (DHAP) to diacylglycerol (DAG), a protein kinase activator - C (PKC), is increased, as also the conversion of triose phosphate to methylglyoxal is increased, the major intracellular precursor of glycation advanced end products (AGE). Excess fructose 6-phosphate is converted to

UDP -N-acetylglucosamine, which increases protein modification, and excess glucose is metabolized through the polyol pathway, where reduced coenzyme (NADPH) is consumed and glutathione (GSH) concentration decreases. Despite all research, the association between these processes remains unknown, and clinical studies on their inhibitors have been disappointing [21,22].

In the development of diabetic microvascular kidney disease, i.e. oxidative cell damage, as well as its progression, the most important role is played by hyperglycemia and activation of the renin-angiotensin-aldosterone system in kidney tissue. Several cell types in the nephron, including podocytes as well as mesangial cells and proximal tubular cells, express GLUT1 glucose transporters that cannot reduce glucose entry into the cell at its high concentrations in the extracellular space. Intracellular hyperglycemia, consequently, causes the formation of reactive oxygen species. Mitochondrial O_2 - diffuses into the cytoplasm where together with hyperglycemia and/or free fatty acids (FFA) contributes to the development of many diabetes-related cell damages. Reactive oxygen species deplete antioxidant protection, using "scavengers" of free radicals and enzymes that detoxify them. If oxygen species are not detoxified, cellular components are damaged and signaling pathways change. The concentration of non-enzymatic antioxidants decreases, but also the activity of enzymes of antioxidant protection [23–25].

The subject of various researches was the examination of the activity of the enzyme glutathione S-transferase in patients with diabetes. In patients with diabetes, levels of glutathione (GSH), a key component of cellular non-enzymatic antioxidant defense system involved in the removal of free radicals and reactive oxygen species, are reduced. Pancreatic β -cells are a potential target for tissue damage induced by oxidative stress, as these cells are sensitive to stress due to low production of antioxidant protection enzymes. Kim

et al. have shown that insulin and growth factors regulate gene expression for enzymes involved in the detoxification processes of electrophilic compounds, including cytochrome P450 (CYP), glutathione S-transferase (GST) and microsomal epoxy hydrolases, and this may partly explain progressive deterioration of β -cell function in DM type 2 [26].

Glutathione transferase

Glutathione transferases (EC 2.5.1.18) (GST) belong to a family of multifunctional enzymes that represent significant participants in the phases II in enzymatic detoxification in the cell. They catalyze the conjugation reaction of tripeptides, glutathione (GSH, γ -glutamyl-cysteinyl-glycine), a peptide compound with a free thiol group, with various electrophilic metabolites of endogenous or exogenous origin, including many carcinogens, drugs, and many products of oxidative metabolism, toxins and allow them to eliminate from the cell. GSTs have a strong antioxidant activity against reactive oxygen species and peroxides. In conjugation with glutathione they reduce the reactivity of electrophilic compounds to biologically important macromolecules, such as proteins and nucleic acids. GSTs also catalyze hormone biosynthesis, peroxide degradation, tyrosine degradation, dehydroascorbate reduction, and many other metabolic reactions. They also participate in cell apoptosis [24].

The distribution of GST isoenzymes is not the same in most tissues, i.e. certain isoenzymes that are highly present in one organ may be absent or present in very low concentrations in other tissues. Therefore, the detoxification processes and harmful effects of electrophilic compounds are largely determined by the appropriate isoenzyme profile of glutathione transferases of these tissues [24].

Isoenzymes represent different forms of one enzyme that catalyze the same reactions.

Different GSTs show different substrate specificity and catalyze different types of chemical transformations. Human GSTs are divided into three families: the cytosolic, mitochondrial, and microsomal families. The cytosolic family of GST is further divided into seven classes, named after the Greek letters, and abbreviated to capital letters: Alpha (GST A, five isoenzymes), Mi (GST M, five isoenzymes), Omega (GST O, two isoenzymes), Pi (GST P, one enzyme), Sigma (GST S, one enzyme), Theta (GST T, two isoenzymes) and Zeta class (GST Z, one enzyme). The classification of cytosolic GSTs was performed on the basis of the primary structure. Members of the same class of GST have more than 40% identical amino acid sequences, while GSTs from different classes have less than 25% identical sequences. Catalytically active proteins are dimers of subunits of the same class. Each subunit has two significant domains in its structure: the *thioredoxin-like N-terminal domain* (G-domain) and the α -helical domain (the so-called H-domain). The G-domain represents the site of reduced glutathione (GSH) binding and it is present in all classes. The sulfur atom from glutathione is linked by a hydrogen bond to the catalytic residues at the N-terminal end of the protein. This bond stabilizes activated GSH and plays the most significant role in the catalytic action of GST [24–27].

Glutathione transferase gene polymorphism and risk of diabetes

GSTs are represented in unique forms in each organ. Different GST isoenzymes are products of GST gene expression, which differ from each other in their structural, physicochemical and immunological properties. Their synthesis is encoded by a number of genes in the human genome, which are grouped on different chromosomes and which are class-specific. So far, 16 genes encoding glutathione transferase of the cytosolic family have been identified in

humans. Functional genetic polymorphisms are present in most of these genes. The most commonly described polymorphisms are genes encoding GSTM1-1, GSTT1-1, and GSTP1-1. The genes encoding the synthesis of all five M classes of GST are grouped on the shorter arm of chromosome 1 (1p13.3), and the genes encoding the synthesis of T class are located on chromosome 22 (22q11.2). Approximately half of members of the white and yellow races are without active alleles (GSTM1 - null genotype), while the lowest frequency of GSTM1 - null genotype (24%) is present in members of the black race. Homozygous deletion of the GSTT1 gene is present in about 20% of white and black people, while the GSTT1-null genotype is most prevalent in members of the yellow race [28,29].

Genetic deficiency of the GSTT1 enzyme appears to be a strong and independent predictor of early vascular morbidity and death in individuals with type 2 diabetes. A number of studies have been published on the association of GST polymorphisms and various diseases, especially in conditions associated with oxidative stress, such as obesity, type 2 diabetes, coronary heart disease, neurodegenerative diseases or smoking habits, cancer, and different responses to chemotherapy. With the discovery of allelic variants of GSTP1 encoding enzymes with reduced catalytic activity, the hypothesis that the combination of GST class M, P, T polymorphisms contributes to the development of the disease, together with environmental factors, has been the subject of many studies [30–36].

The association between GSTT1/GSTM1 deletion polymorphisms and predisposition to diabetes has been the subject of several studies, but there is inconsistency in the results of these studies. Yalin et al. show that this GSTM1 gene polymorphism may contribute to the development of diabetes as well as that the GSTM1 gene may be a useful marker for predicting susceptibility to diabetes mellitus. In their research, no association

was found between the GSTT1-null genotype and the GSTP1-null genotype with the onset of diabetes. Patients with type 2 diabetes mellitus, in the population of northern India, had a higher incidence of GSTM1-null genotype compared to controls, and the presence of GSTM1-null genotype doubled the risk of developing type 2 diabetes. In contrast, studies in some other populations have shown an association between the GSTT1-null genotype and the risk of developing type 2 diabetes, and that the presence of the GSTT1-null genotype and the GSTM1-null/GSTT1-null genotype combination was an independent risk factor for diabetes. Despite differences in literature data, a meta-analysis of the study concluded that GSTT1-null genotype as well as GSTM1-null/GSTT1-null genotype represent risk factors for the development of type 2 diabetes mellitus [37–47].

There is a small number of papers on the association of GST gene polymorphism and microvascular complications of diabetes, and their results are inconsistent. Deletions of GSTM1 and GSTT1 individually or both of them were associated with decreased GST activity and increased oxidative stress in individuals with chronic kidney disease caused by diabetes or non-diabetic etiology. People with the GSTT1-null genotype are more likely to have generalized vasculopathy, with an increased risk of developing diabetic nephropathy and retinopathy, and this association does not depend on smoking status [48,49].

In the human kidney, GSTM classes are mainly localized in the tubules. GSTM1 gene expression has been detected in about 50% of people. This genetic locus is highly polymorphic and the absence of GSTM1 is attributed to homozygous deletion of the gene (null genotype). Class T enzymes are active in the kidneys and liver. The genetic locus for GSTT1 is also polymorphic and the absence of GSTT1 was found in 15–30% of Caucasians and > 50% of Chinese people [35,36,39,40,42,47].

Cilenšek et al. showed that the frequency of GSTT1-null genotype was 2 times higher in patients with diabetic retinopathy, compared to patients without this complication. The absence of GSTM1 is thought to have protective effects on the development of diabetic retinopathy in patients with type 2 diabetes mellitus [47].

Datta et al. indicated that patients with type 2 diabetes with GSTT1 and GSTM1-null genotype have reduced activity of GST enzymes, which can affect the increased production of reactive oxygen species, and that these patients have a higher risk of developing diabetic nephropathy [48,49].

Yang et al. showed that the existence of GSTT1-null genotype is a risk factor for development of diabetic nephropathy, and that homozygous deletion of GSTT1 gene is a risk factor for development of terminal renal failure in patients with diabetes, but not in patients with hypertension as an etiology of this condition. In this study, no association was found between the deletion of the GSTM1 gene and the development of end-stage renal disease in both groups [50].

Kim et al. have demonstrated a positive association of GSTM1-null genotype with the occurrence of diabetic nephropathy, while Fujita et al. proved that the frequency of GSTM1-null genotype was not significantly higher in patients with type 2 diabetes with nephropathy compared to patients without nephropathy, and that the mentioned gene polymorphism did not contribute to the development of diabetic nephropathy in patients with type 2 diabetes mellitus [51,52].

Šuvakov and co-workers showed that people with GSTM1-null genotype had a 1.6-fold higher risk of developing end-stage renal disease than people with GSTM1-active genotype. When GST genotypes were analyzed in combination, individuals who were carriers of the GSTM1-null/GSTT1-null genotype had the highest risk of developing end-stage renal disease. The risk found in carriers of GSTM1-null

and GSTP1 low-activity genotype is also significant. Also, it was shown that certain GST polymorphisms affect increased oxidation of proteins and lipids, where the effect was most pronounced in carriers of GSTM1-null genotype. There was also a strong association between genotypes, with reduced or absent activity of GSTM1, GSTT1, GSTA1, and GSTP1 and susceptibility to oxidative or carbonyl stress in patients with end-stage renal disease [53].

We conducted a study to examine the frequency of GST deletion polymorphisms in the population with diabetes in the eastern part of Bosnia and Herzegovina, and the possible association of these polymorphisms with the development of microvascular complications of diabetes. In this study, the distribution of GSTM1 polymorphic variants did not differ significantly in patients with diabetes compared to the control group, while the GSTT1-null genotype was significantly more common in the group of patients with diabetes compared to the control group. Patients with diabetes were significantly more often carriers of the combined GSTM1-active/GSTT1-null genotype compared to the patients from the control group. Also, the distribution of individual GSTM1 and GSTT1 as well as combined GSTM1/GSTT1 genotypes did not differ significantly in patients with diabetic nephropathy compared to the patients without this complication, while GSTM1 deletion polymorphism was not associated with the risk of developing diabetes. Patients with diabetes, carriers of the GSTT1-null genotype had a 3-fold higher risk of developing diabetes compared with patients carrying the GSTT1-active genotype. A small modifying effect of the GSTM1-active genotype was obtained in patients carrying the combined GSTM1-active/GSTT1-null genotype, in whom the risk of developing diabetes was 3.37-fold higher compared with patients carrying both reference alleles. Further modifying effect of GSTM1 and GSTT1 deletion polymorphisms at risk for diabetic nephropathy was not ob-

tained, although patients with GSTM1-null genotype had a 1.47-fold higher risk of developing nephropathy compared with patients with GSTM1-active genotype, this increase was not statistically significant. No statistically significant risk for nephropathy in patients with diabetes was observed with respect to GSTT1 deletion polymorphism. No combination of GSTM1/GSTT1 genotypes was associated with a significant risk of developing diabetic nephropathy. Although patients with the GSTM1-null/ GSTT1-null genotype had a 2.07-fold higher risk of developing nephropathy, the risk was not statistically significant. In patients with diabetic nephropathy, stratified based on the severity of renal disease, it was shown that patients with end-stage renal disease were significantly more likely to be carriers of the combined GSTM1-null/ GSTT1-null genotype. In patients with diabetes, regardless of the presence of diabetic nephropathy, there is a significant positive correlation between the presence of both GSTM1-null genotype and GSTT1-null genotype and advanced glycation end products in the serum of these patients. Concentrations of late glycation end products (AGEs) were significantly higher in patients carrying either the GSTM1-null or GSTT1-null genotype compared to patients carrying active variants of these genes. Moreover, this association was also obtained in patients carrying the combined GSTM1-null/ GSTT1-null genotype. There were more overweight people in the group of patients with diabetes. Also, in the subgroups of patients with diabetes, the percentage of overweight people was significantly higher than the percentage in the control group. A larger number of subjects in the group of patients with diabetes had hypertension compared to subjects in the control group, which confirms the importance of these risk factors in the development of diabetes. Diabetes lasted significantly longer in patients with diabetic nephropathy compared to the patients without this microvascular complication [3,16].

Conclusion

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus that develops in about a third of patients with DM. Numerous studies have linked the polymorphism of the GST gene to a predisposition to various diseases, including diabetes and diabetic nephropathy.

Funding source. The authors received no specific funding for this work.

Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Studies indicate that genetic variations in enzymes involved in free radical metabolism are associated with the development of terminal renal failure in patients with diabetes. GSTT1-null genotype and GSTM1-null/GSTT1-null genotype are risk factors for the development of type 2 diabetes mellitus. These results allow the development of preventive and early therapeutic strategies in high-risk individuals in a modern concept of personalized medicine.

Conflicts of interest. The authors declare no conflict of interest.

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Značaj polimorfizama glutation transferaza za nastanak dijabetične nefropatije

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Genetički faktori i faktori sredine imaju važnu ulogu u nastanku dijabetes melitusa tip 2 (DM2) i njegovih komplikacija. Dijabetesna nefropatija (DN) jedna je od najčešćih mikroangiopatskih hroničnih komplikacija dijabetesa.

Oksidativni stres nastaje u uslovima povećane produkcije slobodnih radikala i/ili smanjenja aktivnosti enzima antioksidativne zaštite i predstavlja bitnu kariku u složenom mehanizmu nastanka dijabetičnih vaskularnih promjena. Glutation transferaze (GST) su enzimi koji su uključeni u procese metabolizma ksenobiotika i dio su kompleksnih mehanizama antioksidativne zaštite. Brojna istraživanja povezuju polimorfizam gena za GST sa predispozicijom za nastanak različitih bolesti, uključujući dijabetes i dijabetičnu nefropatiju.

Naši i rezultati drugih autora ukazuju na to da su genetske varijacije u enzimima koje su uključene u metabolizam slobodnih radikala povezane sa nastankom terminalne bubrežne insuficijencije kod bolesnika sa dijabetesom, što bi moglo postati osnova za razvoj preventivnih i ranih terapijskih strategija djelovanja kod osoba sa visokim rizikom.

Ključne riječi: dijabetes, dijabetesna nefropatija, polimorfizam glutation transferaza