



Influence of GSTM1, GSTT1 and GSTP1 gene polymorphisms on the appearance of microalbuminuria in type 2 diabetes mellitus patients

DOI: 10.1515/rrlm-2016-0006

Dear Editor,

We wish to provide some perspectives with regard to an article recently published in your journal on polymorphisms of Glutathione S-transferase in glaucoma patients [1]. Glutathione S-transferases (GSTs) are a group of genes, the polymorphisms of which have been reported to be also associated with an increased risk for Diabetes Mellitus (DM) [2], malignant diseases [3], and diabetic retinopathy [4].

Glutathione S-transferases (GSTs) represent a family of multifunctional phase II isoenzymes known for their capacity of catalyzing the conjugation of reduced glutathione with a large variety of electrophilic compounds, including carcinogenic agents and products derived from oxidative stress; it has a major role in neutralizing reactive oxygen species (ROS), and it is part of the cellular protection and detoxifying mechanisms, hence the important antioxidant role [3]. Three of these polymorphisms, namely GSTM1, GSTT1, and GSTP1 have raised special interest, and therefore have been more intensively studied. GST enzymes are coded by at least eight distinct loci: alpha (GSTA), mu (GSTM), kappa (GSTK), omega (GSTO), pi (GSTP), sigma (GSTS), theta (GSTT), and zeta (GSTZ). GSTM1 gene locus is found on the short arm of the first chromosome (1p13.3), and its homozy-

gous deletion causes complete lack of enzymatic activity leading to an inability of producing GSTM1 protein (GSTM1 null). GSTT1 gene is located on chromosome 22q11.2. Deletion of the GSTT1 gene leads to a nonfunctional allele and the persons with homozygous deletion do not present functional enzymatic activity (GSTT1 null). The GSTP1 gene is located on chromosome 11q13. A valine to isoleucine substitution affecting exon 5, codon 105 in the GSTP1 gene leads to a decreased enzymatic activity and a reduction of the capacity of the GST to conjugate reactive electrophilic compounds with glutathione, thereby increasing the risk of lesions induced by free radicals [5].

Diabetic nephropathy (DN) is a common microvascular complication of DM being, along with arterial hypertension, one of the causes that lead to end-stage renal disease and also a major cause of premature morbidity and mortality in diabetic patients. This complication is manifested through an increase in the urinary albumin secretion (albuminuria) which gradually progresses to overt albuminuria and finally leads to renal failure, without the presence of other causes of renal disease. Usually, DN associates other micro- or macrovascular complications [6]. The risk for albuminuria is more importantly correlated with the degree of the glycemic imbalance and the evolution of DM time, but a familial susceptibility also exists, which supports the role of genetic factors in the etiopathogeny of DN. Probably, there is a high number of allelic variants that interact, and together with environmental factors and a metabolic imbalance they could generate an individual susceptibility regarding the relative risk of DN occurrence [7]. Oxidative stress is recognized as a causative

agent in the ethiopathogeny of DN. The ROS level increases in parallel with the degree of oxidative stress and it is responsible for oxidative lesions affecting DNA and proteins having a major role in the pathogenesis of many diseases (tumors, coronary artery disease, diabetes mellitus). Renal involvement is preceded by an imbalance between the oxidative and antioxidant activity and it has been found that the degree of oxidant lesions increases simultaneously with the progression of the disease. The severity of albuminuria is used as a marker for DN and an indicator for systemic lesions of the endothelial cells, although advanced modifications of the renal structures are already present when it occurs [8]. Due to the fact that GSTM1 null, GSTT1 null, and GSTP1 Val alleles are associated with a reduction of enzymatic activity, a hypothesis can be stated according to which inadequate GST enzymes levels in the presence of increased oxidative stress can predispose to microvascular complications such as DN in DM. Our previous studies have suggested that the Val allele of the GSTP1 Ile105Val gene polymorphism correlates with the susceptibility for T2DM but not with the risk for peripheral diabetic neuropathy [2]. Data reported to date regarding correlations between the GSTM1, GSTT1, and GSTP1 Ile105Val gene polymorphisms and albuminuria in patients with diabetes mellitus are relatively rare and inconsistent. Doney et al. proved that the GSTT1 null genotype correlates with a generalized vasculopathy with a subsequently increased risk for DN and retinopathy in patients with T2DM [9]. Hovnik et al. have completed a study in which they included patients with type 1 Diabetes Mellitus (T1DM) and they observed that the presence of GSTM1 gene polymorphism was seen more frequently in patients with diabetic retinopathy but not in case of DN. Also, no statistically significant differences have been shown regarding the frequency of GSTT1 geno-

type polymorphism in patients with T1DM with or without diabetic retinopathy or nephropathy. GSTM1 null and GSTT1 null genotype combinations which are followed by a complete lack of enzymatic activity have not been associated with an increased risk of either diabetic retinopathy or nephropathy [10]. A pertinent meta-analysis regarding the effect of GSTs (GSTM1, GSTT1, and GSTP1) gene polymorphisms on the risk of DN that analyzed 9 publications and included 874 patients with T1DM and T2DM in the study group and 966 in the control group was published in 2015 by J. Orlewski et al. [7]. This meta-analysis showed that the GSTM1 null genotype was statistically correlated with the risk of DN in Asians, but not in Caucasians; also, when only T2DM patients were analyzed no statistically significant correlation was found between the GSTM1 null genotype and DN. The GSTT1 null genotype was not associated with DN even after stratified analysis was performed based on ethnicity, T2DM presence, sample size or presence of diabetic retinopathy. No correlation between the GSTP1 genotype and DN was found in the overall or subgroups analysis published by J. Orlewski et al. [7]. However, authors mentioned that the data obtained must be carefully interpreted due to a large number of confounding factors, the relatively small number of patients included in each study, the ethnic heterogeneity and they consider that further investigations are required for exploring the correlation of the above-mentioned polymorphisms with the risk of DN. Contradictory and inconsistent data obtained from genetic studies leave room for further investigations with the purpose of establishing the role of the polymorphisms of GST genes in the development of microvascular complications in diabetes mellitus, including DN. Discovery of novel genetic markers that can be correlated with the risk for these complications in the context of an increasing worldwide DM prevalence could

help in developing personalized prevention and therapeutic strategies.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgement

This work was funded by an internal research grant from The University of Medicine and Pharmacy from of Tîrgu Mures, number 649/14.01.2016

**Adina Stoian¹, Lavinia Horling²,
Alexandru Schiopu³, Laura Iulia
Barcutean⁴, Mircea Stoian^{5,*}, George
Andrei Crauciuc⁶, Anca Motataianu¹**

1. *Neurology Department, University of Medicine and Pharmacy Tîrgu Mures;*
 2. *Ludwig Maximilians University Munich, Germany;*
 3. *Associate Professor, Lund University Experimental Cardiovascular Research Group CRC 91:12, Jan Waldenströms gata 35, SE-205 02 Malmö Cardiology Department Skane University Hospital Malmö Sweden;*
 4. *Clinical Emergency Hospital Tîrgu Mures, Romania;*
 5. *Mures Clinical County Hospital;*
 6. *Department of Genetics, University of Medicine and Pharmacy Tîrgu Mures;*
- *Corresponding author:** Mircea Stoian
e-mail: stoianmirceadoc@yahoo.com

Received: 13th September 2015; Accepted: 10th December 2016; Published: 14th December 2016.

References

1. Ster AM, Petrisor FM, Stan C, Pop VI. Glutathion S-transferase M1 and T1 polymorphisms in a group of Romanian glaucoma patients, Rev Romana Med Lab. 2015;23(4):506-10. DOI: 10.1515/rrlm-2015-0048.
2. Stoian A, Bănescu C, Bălaşa RI, Moţăţăianu A, Stoian M, Moldovan VG, et al. Influence of GSTM1, GSTT1, and GSTP1 Polymorphisms on Type 2 Diabetes Mellitus and Diabetic Sensorimotor Peripheral Neuropathy Risk, Dis Markers. 2015;2015:638693.
3. Bănescu C, Trifa AP, Voidăzan S, Moldovan VG, Macarie I, Benedek Lazar E, et al. CAT, GPX1, MnSOD, GSTM1, GST T1, GSTP1 genetic polymorphisms in chronic myeloid leukemia: a case-control study. Oxid Med Cell Longev. 2014, 11;2014:875861.
4. Moasser E, Azarpira N, Shirazi B, Saadat M, Geramizadeh B. Genetic polymorphisms of glutathione-s-transferase M1 and T1 genes with risk of diabetic retinopathy in Iranian population. Iran J Basic Med Sci. 2014 May;17(5):351-6.
5. Amer MA, Ghattas MH, Abo-Elmatty DM, Abou-El-Ela SH. Evaluation of glutathione S-transferase P1 genetic variants affecting type-2 diabetes susceptibility and glycemic control, Arch Med Sci. 2012 Sep 8;8(4):631-6. DOI: 10.5114/aoms.2012.30286.
6. Stoian A, Moţăţăianu A, Bajko Z, Maier S, Bărcuţean L, Stoian M, et al. Cardiovascular and renal prognosis in patients with arterial hypertension, type 2 diabetes mellitus and microalbuminuria, HVM Bioflux, 2016, 8(1):45-9.
7. Orlewska J, Orlewska E. Effects of genetic polymorphisms of glutathione S-transferase genes (GSTM1, GSTT1, GSTP1) on the risk of diabetic nephropathy: a meta-analysis. Pol Arch Med Wewn. 2015;125(9):649-58.
8. Shao N, Kuang HY, Wang N, Gao XY, Hao M, Zou W, et al. Relationship between Oxidant/Antioxidant Markers and Severity of Microalbuminuria in the Early Stage of Nephropathy in Type 2 Diabetic Patients. J Diabetes Res. 2013;2013:232404. DOI: 10.1155/2013/232404.

9. Doney AS, Lee S, Leese GP, Morris AD, Palmer CN. Increased cardiovascular morbidity and mortality in type 2 diabetes is associated with the glutathione S-transferase theta-null genotype: a Go-DARTS study. *Circulation*. 2005 Jun 7;111(22):2927-34. DOI: 10.1161/CIRCULATIONAHA.104.509224.
10. Hovnik T, Dolzan V, Bratina NU, Podkrajsek KT, Battelino T. Genetic polymorphisms in genes encoding antioxidant enzymes are associated with diabetic retinopathy in type 1 diabetes. *Diabetes Care*. 2009 Dec;32(12):2258-62. DOI: 10.2337/dc09-0852.