Medicinski podmladak

Medical Youth

MINI REVIEW ARTICLE

GLUTATHIONE TRANSFERASE GENE POLYMORPHISM IN END STAGE RENAL DISEASE

POLIMORFIZAM GLUTATION TRANSFERAZA U TERMINALNOJ BUBREŽNOJ SLABOSTI

Sonja Šuvakov[1], Tatjana Simić[1], Tatjana Damjanovic[2]

[1]University of Belgrade, Faculty of Medicine, Institute of Medical and Clinical Biochemistry, Serbia
[2]Department of Nephrology, Clinical Hospital Centre Zvezdara, Serbia

Correspondence: sonja.suvakov@gmail.com

ABSTRACT

Chronic kidney disease is described as a progressive and irreversible deterioration in kidney function. When there is less than 10% of nephron function pertained, patients face end-stage renal disease, where renal replacement therapy is needed. Data show that the most common method used to treat advanced and permanent kidney failure is hemodialysis. . Increased oxidative stress is a hallmark of end-stage renal disease (ESRD). Glutathione S-transferases (GST) are involved in the detoxification of xenobiotics and protection of oxidative damage. The role of genetic polymorphism of antioxidant enzymes GSTA1, GSTM1, GSTP1 and GSTT1 in susceptibility towards end-stage renal disease development has become prominent recently. Furthermore, GST gene polymorphism may modulate the degree of oxidative stress byproducts in end-stage renal disease patients and, therefore, influence their overall and cause-specific cardiovascular mortality.

Key words:
end-stage renal disease,
glutathione S-transferases,
haemodialysis,
oxidative stress,
polymorphism

The authors declare no conflicts of interest.

doi:10.5937/mp67-12568
Editorial board: podmladak.med.bg@gmail.com

INTRODUCTION

Chronic kidney disease is of major concern all over the world. It is estimated that in U.S. of America, around 10% of adults are suffering from chronic kidney disease (1). Data are showing that incidence of ESRD is progressively growing worldwide in the last twenty years, with more than two million affected individuals and over half million in the Europe. According to national dialysis register, there are almost 6000 people in Serbia treated with some type of renal replacement therapy (2). Incidence of ESRD in Serbia was also growing in the last decade, rising from 107 to 189 patients per million individuals. It is important to note that Serbia is among the European countries with higher incidence of CKD and ESRD.

The main causes of CKD include: diabetes mellitus, hypertension and glomerulonephritis. These three conditions are responsible for more than half of all CKD cases. Among other causes that may affect the renal function are hereditary diseases (polycystic kidney disease), malformations that occur during fetal development and lupus are described. Obstructions (kidney stones, tumors or an enlarged prostate gland in men) and repeated urinary infections are also among common reasons. There are at least two reasons for CKD to be considered as a serious condition: the first one is that these patients are at greater risk to develop cardiovascular complications, tumors and chronic infections; the second one is that majority of CKD patients will develop ESRD, the fifth stage of CKD, where renal replacement therapy is needed. Data have shown that total and cardiovascular mortality in ESRD patients is increased up to 30 fold as compared to general population (3).

Chronic kidney disease (CKD) belongs to the most well characterized oxidative diseases, in terms of the role that free radicals play in its pathogenesis, progression and complications (4,5). Various causes of CKD such as hypertension, diabetes and inflammation (e.g. glomerulonephritis) activate molecular pathways, leading to increased free radical production in the kidneys. Increased ROS production in renal tissue, as described in an elegant review of Vaziri et al.(6), is primarily driven by activation and up-regulation of ROS-producing enzymes, including NAD(P)H oxidase (NOX) isoforms, cycloxygenase-2, lipoxygenase, as well as uncoupled nitric oxide synthase (NOS), mitochondrial dysfunction and endoplasmic reticulum stress (7). Oxidative changes, at molecular and cellular level in the kidney, are accompanied by progressive deterioration of renal function, which occurs through four clinical stages and finally results in renal failure and uremic state, often referred as end stage renal disease (ESRD) (Stage 5). In the course of CKD progression, local oxidative stress in kidneys exerts gradually to systemic level. Namely, impaired renal function leads to accumulation of toxic end-products of exogenous and endogenous origin, which pose a significant electrophilic stress and also enhance pro-oxidant condition. Having reached ESRD, patients require renal replacement therapy, performed either as regular peritoneal or hemodialysis procedures, known to be associated with leukocyte activation, leading to progressive increase in free radical production. Systemic oxidative stress in ESRD is considered to be the cornerstone of atherosclerotic process, which leads to various cardiovascular complications in these patients (6). Despite well described link of oxidative stress with cardiovascular complications in dialysis patients, the role of genetic predisposition in enhanced oxidative damage and consequent worsening of ESRD patients' prognosis remains elusive. Among potential genetic biomarkers of susceptibility to oxidative stress and cardiovascular complications in ESRD, polymorphisms in genes encoding antioxidant enzymes glutathione transferases has emerged recently.

COMMON GST POLYMORPHISMS

Glutathione S-transferases (GSTs) (EC 2.5.1.18) are superfamily of enzymes belonging to phase II enzymes that play an important role in the detoxification reactions (8). GSTs catalyze the conjugation of the tri-peptide glutathione (GSH, γ-glutamylcysteinyl-glycine) with a hydrophobic co-substrate possessing an electrophilic center, in order to produce an inactive hydrophilic conjugate, which is easily excreted from the body. Apart from conjugation with glutathione, GSTs possess non-catalytic activity and the most important one described so far are the role of GSTP1 and GSTM1 in the inhibition of c-Jun N terminal kinase (JNK)(9).

The *GST* genes, located on different chromosomes, are described as highly polymorphic (10,11). Because of their well known xenobiotic-metabolizing activity, genetic variations in *GST* genes have gained much of the attention recently. Any change in the expression of GST protein level might possibly influence an individual's susceptibility to carcinogens and various diseases. The *GSTA1* gene is found on chromosome 6p12. The product of this gene, GSTA1 enzyme, catalyzes the conjugation of glutathione with many electrophilic compounds and possess glutathione-dependent (selenium-independent) peroxidase activity. Three linked base substitutions at positions -567, -69 and -52 are described regarding *GSTA1* gene polymorphism. These substitutions result in two alleles h*GSTA1*A* (-52G, -69C, -567T) and h*GSTA1*B* (-52A, -69T, -567G) (12). Distribution of alleles varies within population. In Caucasians, around 38% possess *GSTA1*A/*A* genotype, 48% *GSTA1*A/*B* genotype and 14% *GSTA1*B/*B* genotype (13). Individuals possessing *GSTA1*B/*B* genotype are usually referred as *GSTA1-low activity* subjects.

The GSTM1 gene is located on chromosome 1p13.3 (14). One of the most studied polymorphisms of *GSTM1* gene is a deletion polymorphism which results in a completely absent enzyme activity. The *GST* mu class has been recognized to metabolize carcinogens from cigarette smoke such as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines (15). About 50% of the Caucasians

are lacking GSTM1 activity and are, therefore, referred as *GSTM1-null* genotype individuals (16).

Gene for GSTP1 is located on chromosome 11q13. The most well described *GSTP1* gene polymorphism represents a result of transition from Ile to Val at codon 105 , a polymorphism that is known as *rs1695* or *GSTP1 Ile-105Val* (17,18). Most of the substrates for GSTP1 protein are different diol epoxides, polycyclic aromatic hydrocarbon (PAHs) found in a cigarette smoke. Therefore, polymorphic expression of *GSTP1* has been linked so far with various cancer developments (19–21). In healthy, white population, the frequencies of the genotype variants of *GSTP1* rs1695 polymorphism are **Ile/*Ile* 51.5%, **Ile/*Val* 39.4% and **Val/*Val* are 9.1%, (22).

The human *GSTT1* gene like *GSTM1*, most commonly exhibits deletion polymorphisms (23). Homozygous deletion of both *GSTT1* alleles represents an *GSTT1-null* genotype, which is mostly associated with development of urinary bladder carcinoma, in individuals exposed to pesticides (24). Heterozygotes, with only one allele absent, may possess lower enzyme activity and are called *GSTT1-active* genotype carriers. Homozygous deletion of *GSTT1* gene is present in about 20% of Caucasians (4).

Genetic polymorphism that affects GST expression results in alteration of enzyme activity profile. Therefore, it is reasonable to expect that individual's antioxidant capacity will differ, depending on particular *GST* genotype and phenotype. From the clinical point of view, deletion and single nucleotide polymorphism of the *GSTA1, GSTM1, GSTP1*, and *GSTT1* genes have been investigated in both malignant and non-malignant disease development. Homozygous deletion of *GSTM1* gene results in absent GSTM1 enzyme activity. Therefore the individuals with GSTM1 deficiency are not able to detoxify broad specter of xenobiotics and metabolic intermediates, which indicates their increased susceptibility towards various disease development. Indeed, GSTM1-null genotype has been the most studied in terms of higher susceptibility towards various cancers and chronic disease development. Among *GST* gene polymorphisms, deletion of both *GSTM1* alleles represents the most prominent risk factor of ESRD development, although the magnitude of OR (odds ratio) differs in terms of ethnicity of studied population (25–28). Since the kidney is the organ in which bio activation of many xenobiotic usually takes place, it is not surprising that *GSTM1* deletion is found to be associated with vulnerable renal parenchyma. Lack of *GSTT*1 activity is also a result of gene deletion. In a similar manner deletion polymorphism of *GSTT1* gene results in increased risk for ESRD development (29), because of inefficient metabolism of many nephrotoxic compounds. Furthermore, the presence of *GSTM1-null* and *GSTT1-null* genotypes in combination is able to further increase the ESRD risk (26,28,30)

Regarding SNP polymorphism of *GSTP1* gene, it is noted that individuals who carry at least one variant allele (so called *GSTP1-low activity* genotype), and are therefore with lower GSTP1 activity, are also affected with increased ESRD risk (25,31). A combination of null/low activity *GSTM1/GSTT1/GSTP1* genotypes further increases the ESRD risk, as it is shown in few studies, although the magnitude of this association differs significantly (25,28).

Since the alpha class possesses the glutathione dependent peroxidase activity and catalytic efficiency towards many lipid peroxidation intermediates, one could expect that individuals with genetic polymorphism of *GSTA1* gene that results in 4-fold lower enzyme activity, would be affected with this polymorphism. However data on the role of *GSTA1-low activity* genotype are limited. There is only one study in which it was shown no association of *GSTA1* polymorphism with higher risk of ESRD development (28).

GST POLYMORPHISMS ARE ASSOCIATED WITH ENHANCED OXIDATIVE STRESS IN ESRD

The origin of increased oxidative stress in ESRD patients includes low molecular weight uremic toxins accumulation, loss of antioxidants and bioincompatibility with dialysis membrane (4,32). Besides well established causes of oxidative stress in ESRD, there is an increasing interest in the role of genetic polymorphisms of *GSTA1*, *GSTM1*, *GSTP1* and *GSTT1*, in contribution to oxidative damage of proteins and lipids in these patients. Thus, data concerning genetic predisposition to worse oxidative phenotype in patients with ESRD are limited. Recently, it has been shown that individual *GST* polymorphisms influence vulnerability to both protein and lipid oxidation, with *GSTM1-null* gene variant, having the most pronounced effect. Specifically, malondialdehyde, most commonly used biomarker of lipid peroxidation, has been unambiguously shown to be elevated in ESRD patients carriers of *GSTM1-null* or *GSTT1-null* genotype (26,28,33). Moreover, it seems that this deleterious effect of null genotype is even more pronounced when *GSTM1 null* and *GSTT1 null* are combined (28). Proteins in plasma of ESRD patients are also oxidatively modified in relation to GST genotypes. It seems that ESRD patients, based on *GST* genotype, may be stratified regarding carbonyl and nitrosative stress (28). In addition, nucleic acid oxidative damage also occurs in patients on hemodialysis. This kind of damage also depends on GST genotype. Namely, Lin et al. showed that ESRD patients with *GSTM1-null* genotype have higher plasma level of 8/OH/deoxy guanosine, well established DNA oxidation biomarker (34). The enhancement of oxidative damage associated with low activity or null *GST* genotypes seems to be biologically plausible, since the up regulation of GST expression and activity observed as reactive phenomenon in uremic milieu (32) cannot reach levels required to enable efficient antioxidant protection of vital macromolecules.

GSTM1 NULL GENOTYPE INFLUENCES CARDIOVASCULAR SURVIVAL IN ESRD

Development of atherosclerosis represents the essential step in cardiovascular complication in ESRD patients which comprises up to 40% of death outcome in this population (3). Results of several studies have revealed the potential role of oxidative stress in atherogenesis (35–37). Since the altered gene expression of GST enzymes influences the level of oxidative damage (28), it is reasonable to assume that it may influence atherosclerotic processes and contribute to cardiovascular complications development. Indeed, the effect of homozygous deletion of *GSTM1* gene in lifelong smokers in Netherland has shown a progression of atherosclerosis in these individuals (38). There is an ongoing discussion in the literature whether the incidence of the coronary artery disease is significantly higher in individuals with *GSTM1-null* and *GSTT1-null* genotypes (39–42) . In addition, in the non-ESRD individuals with *GSTM1* and/or *GSTT1-null* genotypes higher incidence of cardiovascular diseases has been described (30,43). The latest study of Taspinar *et al.* has suggested that deletion of both *GSTM1* and *GSTT1* genes in patients with type 2 diabetes mellitus results in increased susceptibility to advanced atherosclerosis (44). Interestingly, the role of *GST* polymorphism in fatal cardiovascular diseases development in ESRD patients has been addressed in only two studies. Lin *et al*, revealed that ESRD patients with the homozygous *GSTM1* deletion have higher overall mortality rate when compared to those with the *GSTM1-active* genotype (34) In another study association between *GSTM1-null* genotype and specific cardiovascular causes of death, such as myocardial infarction and cerebral vascular insult (CVI) in ESRD has been suggested for the first time (45). The other common GST polymorphisms, such as *GSTA1*, *GSTP1* and *GSTT1*, showed no association with ESRD patients overall or cardiovascular mortality (45).

FURTHER PERSPECTIVES

GST family members play a dual role in defense mechanisms, which counteract complex biochemical changes present in uremic state. Namely, all products of analyzed GST genes possess both glutathione conjugating and antioxidant enzymatic activity. Results on association of common *GST* polymorphisms, with oxidative stress development and its possible implications in prognosis, may lead to new approaches in the individualization of antioxidant therapy in ESRD patients.

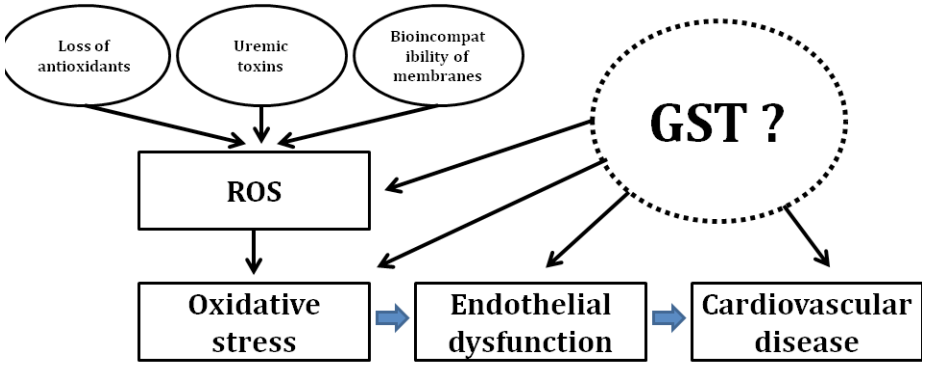

Figure 1. Possible association between glutathione transferase gene polymorphism and oxidative stress and cardiovascular disease

Literature

1. Plantinga LC, Boulware LE, Coresh J, Stevens LA, Miller ER, Saran R, et al. Patient awareness of chronic kidney disease: trends and predictors. Arch Intern Med. 2008;168(20):2268–75.
2. Djukanović L, Aksić-Miličević B, Antić M, Baković J, Varga Ž, Gojaković B, et al. Epidemiology of end-stage renal disease and hemodialysis treatment in Serbia at the turn of the millennium. Hemodial Int Int Symp Home Hemodial. 2012;16(4):517–25.
3. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol JASN. 1998 Dec;9(12 Suppl):S16-23.
4. Libetta C, Sepe V, Esposito P, Galli F, Dal Canton A. Oxidative stress and inflammation: Implications in uremia and hemodialysis. Clin Biochem. 2011;44(14–15):1189–98.
5. Kao MPC, Ang DSC, Pall A, Struthers AD. Oxidative stress in renal dysfunction: mechanisms, clinical sequelae and therapeutic options. J Hum Hypertens. 2010;24(1):1–8.
6. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. Nat Rev Nephrol. 2010;6(5):287–96.
7. Malhotra JD, Kaufman RJ. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxid Redox Signal. 2007;9(12):2277–93.
8. Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev Pharmacol Toxicol. 2005;45:51–88.
9. Adler V, Yin Z, Fuchs SY, Benezra M, Rosario L, Tew KD, et al. Regulation of JNK signaling by GSTp. EMBO J. 1999;18(5):1321–34.
10. Krajka-Kuźniak V, Szaefer H, Baer-Dubowska W. Hepatic and extrahepatic expression of glutathione S-transferase isozymes in mice and its modulation by naturally occurring phenolic acids. Environ Toxicol Pharmacol. 2008;25(1):27–32.
11. Oakley AJ. Glutathione transferases: new functions. Curr Opin Struct Biol. 2005;15(6):716–23.
12. Morel F, Rauch C, Coles B, Le Ferrec E, Guillouzo A. The human glutathione transferase alpha locus: genomic organization of the gene cluster and functional characterization of the genetic polymorphism in the hGSTA1 promoter. Pharmacogenetics. 2002;12(4):277–86.
13. Magagnotti C, Pastorelli R, Pozzi S, Andreoni B,

Fanelli R, Airoldi L. Genetic polymorphisms and modulation of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-DNA adducts in human lymphocytes. Int J Cancer. 2003 20;107(6):878–84.
14. Ross VL, Board PG, Webb GC. Chromosomal mapping of the human Mu class glutathione S-transferases to 1p13. Genomics. 1993;18(1):87–91.
15. Ketterer B, Harris JM, Talaska G, Meyer DJ, Pemble SE, Taylor JB, et al. The human glutathione S-transferase supergene family, its polymorphism, and its effects on susceptibility to lung cancer. Environ Health Perspect. 1992;98:87–94.
16. Benhamou S, Lee WJ, Alexandrie A-K, Boffetta P, Bouchardy C, Butkiewicz D, et al. Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis. 2002;23(8):1343–50.
17. Ali-Osman F, Akande O, Antoun G, Mao JX, Buolamwini J. Molecular cloning, characterization, and expression in Escherichia coli of full-length cDNAs of three human glutathione S-transferase Pi gene variants. Evidence for differential catalytic activity of the encoded proteins. J Biol Chem. 1997;272(15):10004–12.
18. Watson MA, Stewart RK, Smith GB, Massey TE, Bell DA. Human glutathione S-transferase P1 polymorphisms: relationship to lung tissue enzyme activity and population frequency distribution. Carcinogenesis. 1998;19(2):275–80.
19. Chen Y-L, Tseng H-S, Kuo W-H, Yang S-F, Chen D-R, Tsai H-T. Glutathione S-Transferase P1 (GSTP1) gene polymorphism increases age-related susceptibility to hepatocellular carcinoma. BMC Med Genet. 2010;11:46.
20. Harries LW, Stubbins MJ, Forman D, Howard GC, Wolf CR. Identification of genetic polymorphisms at the glutathione S-transferase Pi locus and association with susceptibility to bladder, testicular and prostate cancer. Carcinogenesis. 1997;18(4):641–4.
21. Chan QKY, Khoo U-S, Ngan HYS, Yang C-Q, Xue W-C, Chan KYK, et al. Single nucleotide polymorphism of pi-class glutathione s-transferase and susceptibility to endometrial carcinoma. Clin Cancer Res Off J Am Assoc Cancer Res. 2005;11(8):2981–5.
22. Garte S, Gaspari L, Alexandrie AK, Ambrosone C, Autrup H, Autrup JL, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2001;10(12):1239–48.
23. Webb G, Vaska V, Coggan M, Board P. Chromosomal localization of the gene for the human theta class glutathione transferase (GSTT1). Genomics. 1996;33(1):121–3.
24. Matic M, Pekmezovic T, Djukic T, Mimic-Oka J, Dragicevic D, Krivic B, et al. GSTA1, GSTM1, GSTP1, and GSTT1 polymorphisms and susceptibility to smoking-related bladder cancer: a case-control study. Urol Oncol. 2013;31(7):1184–92.
25. Agrawal S, Tripathi G, Khan F, Sharma R, Baburaj VP. Relationship between GSTs gene polymorphism and susceptibility to end stage renal disease among North Indians. Ren Fail. 2007;29(8):947–53.
26. Datta SK, Kumar V, Ahmed RS, Tripathi AK, Kalra OP, Banerjee BD. Effect of GSTM1 and GSTT1 double deletions in the development of oxidative stress in diabetic nephropathy patients. Indian J Biochem Biophys. 2010;47(2):100–3.
27. Gutiérrez-Amavizca BE, Orozco-Castellanos R, Ortíz-Orozco R, Padilla-Gutiérrez J, Valle Y, Gutiérrez-Gutiérrez N, et al. Contribution of GSTM1, GSTT1, and MTHFR polymorphisms to end-stage renal disease of unknown etiology in Mexicans. Indian J Nephrol. 2013;23(6):438–43.
28. Suvakov S, Damjanovic T, Stefanovic A, Pekmezovic T, Savic-Radojevic A, Pljesa-Ercegovac M, et al. Glutathione S-transferase A1, M1, P1 and T1 null or low-activity genotypes are associated with enhanced oxidative damage among haemodialysis patients. Nephrol Dial Transplant. 2013;28(1):202–12.
29. Yang Y, Kao M-T, Chang C-C, Chung S-Y, Chen C-M, Tsai JJP, et al. Glutathione S-transferase T1 deletion is a risk factor for developing end-stage renal disease in diabetic patients. Int J Mol Med. 2004;14(5):855–9.
30. Nomani H, Mozafari H, Ghobadloo SM, Rahimi Z, Raygani AV, Rahimi MA, et al. The association between GSTT1, M1, and P1 polymorphisms with coronary artery disease in Western Iran. Mol Cell Biochem. 2011;354(1–2):181–7.
31. Tiwari AK, Prasad P, B K T, Kumar KMP, Ammini AC, Gupta A, et al. Oxidative stress pathway genes and chronic renal insufficiency in Asian Indians with Type 2 diabetes. J Diabetes Complications. 2009;23(2):102–11.
32. Galli F, Piroddi M, Bartolini D, Ciffolilli S, Buoncristiani E, Ricci G, et al. Blood thiol status and erythrocyte glutathione-S-transferase in chronic kidney disease patients on treatment with frequent (daily) hemodialysis. Free Radic Res. 2014;48(3):273–81.
33. Nomani H, Hagh-Nazari L, Aidy A, Vaisi-Raygani A, Kiani A, Rahimi Z, et al. Association between GSTM1, GSTT1, and GSTP1 variants and the risk of end stage renal disease. Ren Fail. 2016;1–7.
34. Lin Y-S, Hung S-C, Wei Y-H, Tarng D-C. GST M1 Polymorphism Associates with DNA Oxidative Damage and Mortality among Hemodialysis Patients. J Am Soc Nephrol. 2009;20(2):405–15.
35. Madamanchi NR, Zhou R-H, Vendrov AE, Niu X-L, Runge MS. Does oxidative DNA damage cause atherosclerosis and metabolic syndrome?: new insights into which came first: the chicken or the egg. Circ Res. 2010 Oct 15;107(8):940–2.
36. Madamanchi NR, Hakim ZS, Runge MS. Oxidative stress in atherogenesis and arterial thrombosis: the disconnect between cellular studies and clinical outcomes. J Thromb Haemost JTH. 2005;3(2):254–67.
37. Runge MS, Molnar K, Madamanchi NR. "Old" hearts and arteries: the role of oxidative stress. Trans Am Clin Climatol Assoc. 2010;121:52-58-60.
38. de Waart FG, Kok FJ, Smilde TJ, Hijmans A, Wollersheim H, Stalenhoef AFH. Effect of glutathione S-transferase M1 genotype on progression of atherosclerosis in lifelong male smokers. Atherosclerosis. 2001;158(1):227–31.
39. Bhat MA, Gandhi G. Association of GSTT1 and GSTM1 gene polymorphisms with coronary artery disease in North Indian Punjabi population: a case-control study. Postgrad Med J. 2016;
40. Kadıoğlu E, Taçoy G, Özçağlı E, Okyay K, Akboğa MK, Çengel A, et al. The role of oxidative DNA damage and GSTM1, GSTT1, and hOGG1 gene polymorphisms in coronary artery disease risk. Anatol J Cardiol. 2016 Apr 26;
41. Zhang Z-X, Zhang Y. Glutathione S-transferase M1 (GSTM1) null genotype and coronary artery disease risk: a meta-analysis. Int J Clin Exp Med. 2014;7(10):3378–84.
42. Yeh H-L, Kuo L-T, Sung F-C, Chiang C-W, Yeh C-C. GSTM1, GSTT1, GSTP1, and GSTA1 genetic variants are not associated with coronary artery disease in Taiwan. Gene. 2013;523(1):64–9.
43. Ramprasath T, Senthil Murugan P, Prabakaran AD, Gomathi P, Rathinavel A, Selvam GS. Potential risk

modifications of GSTT1, GSTM1 and GSTP1 (glutathione-S-transferases) variants and their association to CAD in patients with type-2 diabetes. Biochem Biophys Res Commun. 2011;407(1):49–53.
44. Taspinar M, Aydos S, Sakiragaoglu O, Duzen IV, Yalcinkaya A, Oztuna D, et al. Impact of Genetic Variations of the CYP1A1, GSTT1, and GSTM1 Genes on the Risk of Coronary Artery Disease. DNA Cell Biol. 2012;31(2):211–8.
45. Suvakov S, Damjanovic T, Pekmezovic T, Jakovljevic J, Savic-Radojevic A, Pljesa-Ercegovac M, et al. Associations of GSTM1*0 and GSTA1*A genotypes with the risk of cardiovascular death among hemodialyses patients. BMC Nephrol. 2014;15:12.