Effect of GSTM1 and GSTT1 Deletions in the Development of Oxidative Stress in Children with Chronic Kidney Disease

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Effect of GSTM1 and GSTT1 Deletions in the Development of Oxidative Stress in Children with Chronic Kidney Disease

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Background: 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 from oxidative damage. We hypothesized that genetic polymorphisms in antioxidant enzymes GSTM1 and GSTT1 are more frequent in ESRD and modulate the degree of oxidative stress in these patients. *Objectives:* The present study was designed to evaluate oxidized LDA (ox-LDL), high-sensitivity C-reactive protein (hs-CRP), and homocysteine (hcy) levels in children with end-stage renal disease (ESRD) treated with maintenance haemodialysis (MHD) or under conservative treatment, to compare these levels with those assayed in control subjects, and to evaluate these levels with different GSTM1 and GSTT1 genotypes. *Methods:* This case-control study was conducted in 78 children. They were divided into 3 groups: group I (44 on HD), group II (14 on conservative treatment), and group III (20 normal healthy children) served as controls. All enrolled cases and controls were subjected to genotyping for GSTM1 and GSTT1 by polymerase chain reaction (PCR) and determination of ox-LDL, hs-CRP, and hcy levels. *Results:* Oxidized LDL levels were significantly higher in both the MHD and conservative treatment groups than in controls and levels were higher in the MHD group than in the conservative treatment group (199.48 ± 78.63 μ/l, 182.07 ± 128.77 μ/l, and 88.25 ± 23.02 μ/l, respectively). hs-CRP levels were significantly higher in the MHD group compared to the control group (4.03 ± 4.59 mg/dl and 1.14 ± 0.75 mg/dl). Homocysteine showed significantly higher levels in the MHD group when compared to both conservative treatment and control groups (73.43 ± 35.08, 20.35 ± 32.81 μmol/ml, and 5.9 ± 2.8 μmol/ml, respectively). Dialyzed and conservative-treatment patients had significantly higher frequencies of the GSTM1 and GSTT1 null genotypes when compared to the control group. *Conclusion:* Patients with GSTM1 or GSTT1 null genotypes are more vulnerable to oxidative stress compared with those who possess normal gene expression in chronic kidney disease. **J Clin Basic Cardiol 2013; 16 (online): 1–5.**

Key words: oxidative stress, chronic kidney disease, children, GSTM1, GSTT1, gene polymorphism, homocysteine

There is a 10–20-fold elevated risk of cardiovascular mortality in patients with end-stage renal disease (ESRD) [1]. Oxidative stress and atherothrombotic vascular disease are associated with high mortality in patients treated with haemodialysis (HD). Alterations of oxidized LDL (ox-LDL) and homocysteine (hcy) levels are important participating agents in the initiation and progression of oxidative and atherogenic events [1]. Several inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), have been shown to independently predict mortality in ESRD patients [2]. As CRP is so strongly associated with vascular disease, it has been suggested that this hepatic-derived protein is not only a marker but also a mediator of vascular disease [2].

Adverse effects of xenobiotics, which are foreign substances, are excreted via covalent interactions between intermediate metabolites and genetic materials or proteins and their related metabolites [3]. Enzymatic reactions of xenobiotic metabolism are needed to avoid accumulation of lipophilic xenobiotics in cells and tissues. These reactions can be divided into 2 phases during the activation-deactivation sequence, namely phase-I and phase-II enzymatic reactions. The key enzyme systems catalyzing phase-I oxidative metabolism are enzymes of the cytochrome P450 (CYP) superfamily. During these reactions, toxic metabolites are generated which might be processed by phase-II enzymes [3].

Phase-II enzymes complete detoxification by neutralizing reactive electrophiles or by acting as indirect antioxidants [4]. NQO1 and GSTs are both phase-II detoxifying enzymes which play important roles in preventing carcinogen-induced disorders [4].

Glutathione S transferase M1 (GSTM1) and glutathione S transferase T1 (GSTT1) are cancer susceptibility genes because of their ability to regulate the conjugation of carcinogenic compounds to excretable hydrophilic metabolites. Deletion variants lacking in enzyme activity exist for both genes [5]. Individuals with homozygous deletions in the GSTM1 or GSTT1 genes are supposed to have less ability to metabolize carcinogens and may therefore be more susceptible to cancers [5].

There is increasing evidence for the presence of disordered oxidative and glycoxidative chemistry in patients who undergo maintenance haemodialysis (MHD) that may contribute to poor cardiovascular and overall outcome. DNA, in particular, is more susceptible to attack by reactive oxygen species (ROS) than proteins and membrane lipids, which are protected against oxidation by low-molecular-weight antioxidants as well as antioxidant enzymes [6].

Altered GST activity associated with polymorphisms is expected to affect cancer risk through decreased protection against DNA damage from reactive electrophiles. GSTs are expressed and have significant activity in the kidney, but few studies have considered GSTs as a susceptibility to renal carcinoma [7].

The aim of the study is to evaluate ox-LDL, hs-CRP, and hcy levels in children with ESRD treated with maintenance haemodialysis (MHD) or under conservative treatment, to compare these levels with those assayed in control subjects, and to evaluate these levels with different GSTM1 and GSTT1 genotypes.

Material and Methods

58 paediatric patients with advanced chronic renal disease (stages 4 and 5 based on estimated glomerular filtration rate [eGFR] according to the National Kidney Foundation classification) [8] were included in the study. They were divided

into 2 groups undergoing conservative treatment (n = 14) or MHD (n = 44). MHD children were selected from the haemodialysis unit of the Center of Pediatric Nephrology and Transplantation (CPNT), whereas children undergoing conservative treatment were selected from the paediatric nephrology clinic, Children's Hospital, Cairo University. The study was performed from April 2012 to December 2012. In conservative-treatment patients, the causes of renal failure were renal hypoplasia or dysplasia, obstructive uropathies, neurogenic bladder, unknown, or metabolic. In MHD, the causes of renal failure were hereditary nephropathies, obstructive uropathies, neurogenic bladder, glomerulopathy, renal hypoplasia or dysplasia, and unknown causes.

Inclusion criteria for MHD patients comprised patients with onset of haemodialysis < 16 years with at least 6 months MHD duration. They were treated with haemodialysis for 3–4 h 3× a week with a polysulfone membrane using bicarbonate-buffered dialysate. Duration of haemodialysis was 1.59–2.75 years. MHD patients and conservative-treatment patients were taking antihypertensive drugs.

All control children (n = 20) were healthy with no clinical signs of vascular or renal disease and no family history of renal disease. Informed consent for genetic studies was obtained from parents of all participants. The protocol of the study was read and approved by the Ethics Committee of the National Research Center (NRC) in Egypt. No CKD patient in any group had cardiovascular events on the basis of examination and detailed clinical history. Additional exclusion criteria were liver disease and nephrotic syndrome (defined as daily proteinuria > 3.5 g/1.73 m^2).

All subjects in the study were subjected to medical history-taking, thorough clinical examination, determination of serum levels of hs-CRP, ox-LDL, hcy, and genotyping for GSTT1 and GSTM1. Three ml of venous blood were collected in EDTA vials for the extraction of genomic DNA.

Determination of hs-CRP in serum was performed by solid-phase, chemiluminescent, immunometric assay (Immulite/Immulite 1,000; Siemens Medical Solution Diagnostics, Eschborn, Germany) [9].

Oxidized LDL was measured in plasma samples by means of a commercially available capture ELISA kit (Mercodia, Uppsala, Sweden). The antibody used in the kit was the murine monoclonal antibody, and the assay was based on the direct sandwich technique, in which 2 monoclonal antibodies are directed against separate antigenic determinants on the oxidized apolipoprotein B moiety of LDL. Absorbance values were read spectrophotometrically at 450 nm [10].

Homocysteine, a modified sulfur amino acid known as a potential risk factor for cardiovascular disease that is increased above normal levels in > 90 % of uremic patients, was measured in plasma samples by means of a commercially available ELISA kit (Diazyme Laboratories, Germany) [11].

Detection of GSTT1 and GSTM1 Polymorphisms

Genomic DNA used was extracted from lymphocytes using the QIAamp DNA Mini isolation kit (QIAGEN, # 51304).

Polymorphic deletion of the GSTT1 gene was determined by amplification in a 50-μl reaction containing each of the primers F 46 (5'-GCCCTGGCTAGTTGCTGAAG) and R 137 (5'-GCATCTGATTTGGGGACCACA). The PCR cycle was 94 °C for 4 min; 94 °C for 15 sec, 59 °C for 30 sec, 72 °C for 45 sec for 35 cycles, followed by 72 °C for 7 min. The presence of 1 or 2 GSTT1 alleles identified by the presence of a 112-bp fragment, or complete deletion (null genotype), was visualized by electrophoresis on a 1.5-% agarose gel.

Polymorphic deletion of the GSTM1 gene was determined by amplification in 50-μl reaction volume containing

P1 (5'-CGCCATCTTGTGCTACATTGCCCG), P2 (5'-ATCTTCTCCTCTTCTGTCTC), and P3 (5'-TTCTGGATTGTAGCAGATCA). The PCR cycle was 94 °C for 4 min; 94 °C for 30 sec, 58 °C for 1 min, 72 °C for 1 min for 35 cycles, followed by 72 °C for 7 min. P1 and P3 amplify a 230-bp product that is specific to GSTM1. The presence of one or both GSTM1, identified by a 230-bp fragment, or its complete deletion (null genotype), was visualized by 1.5-% agarose gel electrophoresis [3].

Statistical Analysis

The Statistical Package for Social Science (SPSS, Chicago, IL, USA) programme, version 11.0, was used for data analysis. Data were summarized as mean ± SD, range or percentage. Data were evaluated between the experimental groups by 1-way analysis of variance (ANOVA). Comparison between patients and the control group was performed by t-test (quantitative variables) and Chi-squared test (qualitative variables). $P < 0.05$ was considered significant.

Results

This case-control study included 24 male (54.5 %) and 20 female (45.5 %) patients, their ages ranged from 5–18 yrs (mean 10.41 ± 3.32). Group II included 8 males (57.1 %) and 6 females (42.9 %), their ages ranged from 2–18 yrs (mean 11.21 ± 4.81). Group III included 14 males (70.0 %) and 6 females (30.0 %), their ages ranged from 4–18 yrs (mean 9.1 ± 3.05).

There were no significant differences between groups with respect to age and sex ratios while oxidized LDL levels were significantly higher both in the MHD and conservative treatment groups than in controls and the levels were higher in MHD group than in the conservative treatment group (199.48 ± 78.63 μ/l, 182.07 ± 128.77 μ/l, and 88.25 ± 23.02 μ/l, respectively). hs-CRP levels were significantly higher in the MHD group compared to the control group (4.03 ± 4.59 mg/dl vs 1.14 ± 0.75 mg/dl). Homocysteine showed significantly higher levels in the MHD group when compared to both conservative-treatment and control groups (73.43 ± 35.08 μmol/ml, 20.35 ± 32.81 μmol/ml, and 5.9 ± 2.8 μmol/ml, respectively; Table 1).

Frequencies of GSTM1 and GSTT1 normal and null genotypes among studied groups are shown in Table 2, dialyzed and conservative-treatment patients had significantly higher frequencies of the GSTM1 null genotype when compared to the control group ($p < 0.000$ and $p < 0.000$, respectively) and the frequency of the null genotype of the dialysis group is higher than that of the conservative-treatment group, yet it did not reach significance. For GSTT1 genotypes, there is increased frequency of null genotype among the dialysis and conservative-treatment groups when compared to the control group ($p < 0.000$ and $p < 0.05$, respectively).

Clinical and biochemical characteristics of CKD patients with different GSTM and GSTT genotypes are shown in Table 3. There were no significant differences regarding age, sex, and hs-CRP levels between both normal and null expressions of GSTM1 and GSTT1 genes in both the MHD and conservative treatment groups. Levels of serum-oxidized LDL showed a significant difference between normal and null expression of both GSTM1 and GSTT1 genes: it was higher in both null GSTM1 and GSTT1 expressions ($p < 0.05$ and $p < 0.000$, respectively), while in the conservative treatment group, it showed a highly significant difference between normal and null GSTT1 expression only ($p < 0.000$). Homocysteine levels were significantly higher for null expression of GSTM1 in the MHD group ($p < 0.05$), they were also higher in the null expression of GSTT1 in the MHD group,

Table 1. Clinical and biochemical characteristics of the studied groups (mean ± SD).

	MHD	CT	Control
n	44	14	20
Age (yrs)	10.41 ± 3.32	11.21 ± 4.81	9.1 ± 3.05
Sex (m/f)	24 (54.5 %)	8 (57.1 %)	14 (70 %)
	20 (45.5 %)	6 (42.9 %)	6 (30 %)
Ox-LDL (μ/l)	199.48 ± 78.63[ac]	182.07 ± 128.77[b]	88.25 ± 23.02
hs-CRP (mg/dl)	4.03 ± 4.59[a]	2.82 ± 3.32	1.14 ± 0.75
Hcy (μmol/ml)	73.43 ± 35.08[ac]	20.35 ± 32.81	5.9 ± 2.8

Data were evaluated by ANOVA test. Values are presented as mean ± SD or percentage as applicable. MHD: maintenance haemodialysis; CT: conservative treatment; Ox-LDL: oxidized LDL; hs-CRP: high-sensitivity C-reactive protein; hcy: homocysteine. [a] HD vs control; [b] CT vs control $p < 0.000$; [c] HD vs CT $p < 0.000$

Table 2. Frequencies of GSTM1 and GSTT1 normal and null types among studied groups

	MHD	CT	Control
n	44	14	20
GSTM1			
Normal	13 (29.5 %)	5 (35.7 %)	20 (100 %)
Null	31 (70.5 %)[a]	9 (64.3 %)[b]	0 (0 %)
GSTT1			
Normal	24 (54.5 %)	10 (71.4 %)	20 (100 %)
Null	20 (45.5 %)[a]	4 (28.6 %)[b]	0 (0 %)

Data were evaluated by Chi-squared test. Values are presented as percentage. MHD: maintenance haemodialysis; CT: conservative treatment. [a] HD vs control; [b] CT vs control; [c] HD vs CT

Table 3. Age, Ox-LDL, hs-CRP, and homocysteine in chronic kidney disease patients with different GSTM and GSTT genotypes

	MHD				CT			
	GSTM1		GSTT1		GSTM1		GSTT1	
	Normal	Null	Normal	Null	Normal	Null	Normal	Null
n	13	31	24	20	5	9	10	4
Age (ys)	9.92 ± 3.01	10.61 ± 3.47	10.29 ± 3.18	10.55 ± 3.56	12.0 ± 5.47	10.78 ± 4.35	10.9 ± 5.10	12.0 ± 3.55
Ox-LDL (μ/l)	158.7 ± 34.9	216.5 ± 85.7*	161.8 ± 34.8	244.8 ± 92.7*	134.0 ± 68.7	208.7 ± 149.4	116.9 ± 55.4	345.0 ± 114.4*
hs-CRP (mg/dl)	4.51 ± 3.94	3.83 ± 4.88	3.58 ± 3.40	4.58 ± 5.76	4.0 ± 4.93	2.17 ± 2.1	3.82 ± 3.62	0.85 ± 1.05
Homocysteine (μmol/ml)	51.3 ± 29.01	82.7 ± 33.58*	64.87 ± 31.43	83.7 ± 37.23	7.2 ± 1.64	27.68 ± 39.7	17.2 ± 29.92	28.25 ± 43.81

Significance was estimated using the independent t-test. Data are mean ± SD. Ox-LDL: oxidized LDL; hs-CRP: high-sensitivity C-reactive protein. * P significant if < 0.05

and higher in the null expression of both GSTM1 and GSTT1 of the conservative treatment group, yet this did not reach statistical significance. In the control group, there was 100 % normal expression of both GSTM1 and GSTT1 genes.

Discussion

Renal disease is associated with a graded increase in oxidative stress markers even in early CKD. This could be the consequence of an increase in reactive oxygen species as well as a decrease in antioxidant defense. This oxidative stress can accelerate renal injury progression [12]. Genetic variants that affect the capacity to handle oxidative stress may therefore influence the outcome of kidney disease [13].

Increased cardiovascular morbidity and mortality are present across the whole renal dysfunction spectrum even in patients with moderate renal insufficiency. In fact, most patients with CKD die of cardiovascular causes rather than progress to end-stage renal disease in which cardiovascular mortality is 15–30 % higher compared to age-adjusted control groups. This high risk of cardiovascular disease seems to be the consequence of a higher prevalence of risk factors in patients with CKD than in the general population [14].

We examined whether genetic variants of GSTM1 and GSTT1 genes, members of a superfamily of glutathione S transferases, influence the course of kidney disease progression in participating Egyptian children. In addition, investigations in which ox-LDL, hs-CRP, and hcy are considered together as important agents involved in the development of oxidative and atherogenic events in end-stage renal disease are limited.

In this study, oxidized LDL levels were significantly higher in both the MHD and conservative-treatment groups than in controls and levels were higher in the MHD group, hs-CRP levels were significantly higher in the MHD group compared to the control group and homocysteine showed significantly higher levels in the MHD group when compared to both the conservative-treatment and control groups. Mahrooz et al [1] included non-diabetic HD patients in their study and found that ox-LDL levels were significantly increased both before and after HD compared with the control group and homocysteine levels in ESRD patients were higher than control subjects both in pre-dialysis and post-dialysis. There was a significantly positive correlation between ox-LDL and homocysteine in samples obtained before HD.

Osorio et al [15] studied atherogenesis markers in patients with stage-5D chronic kidney disease (CKD-5D) on haemodialysis to determine which parameters are modified and whether their behaviour differs between male and female patients of similar age. They found that CKD-5D patients had significantly lower cholesterol, LDL, and ox-LDL levels and significantly higher hcy levels compared to their respective controls. The reduction in ox-LDL in CKD patients does not imply a lower risk of atherosclerosis. In fact, the risk may be higher due to a greater capture of ox-LDL by macrophage scavenger receptors, which are increased in these patients. Elevated hcy levels may also be a risk factor for atherosclerosis in male and female CKD-5D patients.

Helal et al [16] studied HD patients displaying a marked atherogenic profile, as tested by increased levels of total cholesterol, triglycerides, low-density lipoprotein-cholesterol, apolipoprotein A, CRP, hcy, and lower concentrations of high-

density lipoprotein-cholesterol. The same biological disorders found in HD patients were noted in peritoneal-dialysis patients. The peculiar metabolic changes observed by Helal et al [16] confirm the marked tendency of patients with impaired renal function for developing cardiovascular diseases irrespective of the type of dialysis. Shojaei et al [17] investigated patients with maintenance haemodialysis who were taking atorvastatin or lovastatin, vitamin B$_6$, and folic acid for at least 6 months. They found that homocysteine levels were 33 % higher on average than the reference value. Lahrach et al [18] found that haemodialysis patients had more frequently atherogenic dyslipidaemia, hyperhomocysteinaemia, and elevated hs-CRP levels when compared to controls.

In this study, GSTM1 null and GSTT1 null genotypes were significantly higher in both haemodialysis and conservative-treatment groups when compared to controls, indicating that these genotypes may be risk factors for ESRD in children with CKD. Such an association was observed earlier by others [19] who determined GSTM1 and GSTT1 genotypes in ESRD patients. Markers of protein and lipid oxidative damage, together with total oxidant status and pro-oxidant-antioxidant balance were determined: they found that individual GST polymorphisms influence vulnerability to both protein and lipid oxidation, with the GSTM1 null gene variant having the most pronounced effect. They also found that when patients were stratified according to GSTM1 and GSTT1 the highest oxidant damage was noted in those with the GSTM1 null/GSTT1 null genotype.

Datta et al [20] studied 3 groups of Indian patients (diabetics without CKD, diabetic CKD, and non-diabetic CKD), revealing that GSTM1 and GSTT1 deletions singly or together were associated with lower GST levels and higher oxidative stress in both diabetic and non-diabetic CKD and that GSTT1 deletion appears to be associated with both diabetic and non-diabetic CKD irrespective of the GSTM1 status.

Lin et al [6] found that among MHD patients, GSTM null genotype approximately doubled the risk for all-cause mortality during the mean follow-up of 34 months.

Agrawal et al [21] who assessed GSTT1 and GSTM1 polymorphisms in patients with ESRD from North India found that the GSTM1 null genotype was present in 46.74 % of ESRD patients while the GSTT1 null genotype was present in 58.7 % of ESRD subjects. There was a significant association of null alleles of the GSTM1 and GSTT1 with end-stage renal disease.

Yang et al [22] used multiplex PCR to analyze GSTM1 and GSTT1 polymorphisms. To determine their role in the development of ESRD in diabetic and hypertensive patients they revealed that homozygous deletion of the GSTT1 gene is a risk factor for developing ESRD in diabetic patients but not in hypertensive patients.

In this study, regarding the correlation between oxidative stress markers and the different GSTM1 and GSTT1 polymorphisms in end-stage renal disease patients, ox-LDL levels were significantly higher in the null genotypes of both GSTM1 and GSTT1 genes compared to normal gene expression in the MHD group while this significance was found only in GSTT1 null genotype in the conservative treatment group, also homocysteine levels were significantly higher in the null expression of GSTM1 in the MHD group only, it was also higher in the null expression of GSTT1 of the MHD group, and higher in the null expression of both GSTM1 and GSTT1 of the conservative treatment group, yet it did not reach clinical significance.

Martin et al [23] studied the effect of NQO1, GSTM1, and GSTT1 polymorphisms in coronary heart disease and biomarkers of oxidative stress. They revealed that among the entire population individuals with a GSTM1 null polymor-phism have slightly higher hcy levels than those with the wild type but when these data were segregated by case vs control, hcy levels were significantly higher in GSTM1 null subjects in the control group and none of the other biomarkers showed significant variations between GSTM1 or GSTT1 genotypes.

In summary, GSTM1 and GSTT1 null genotypes showed a significantly higher frequency in children with CKD, both on MHD and on conservative treatment. These results suggest that the GST gene polymorphism can serve as a useful genetic marker for evaluation of susceptibility to chronic renal failure. However, the interactions between this genetic predisposition and environmental factors as well haplotype analysis warrant more studies.

Conflict of Interest

The authors declare that they have no competing interests.

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