Role of Donors and Recipients' Glutathione S-Transferase Gene Polymorphisms in Association of Oxidative Stress With Delayed Graft Function in Kidney Allograft Recipients

Jalal Azmandian,[1,2] Ali Mandegary,[3,4] Mahboobeh Pootari,[5] Mohamad-Hadi Nematolahi,[6] Mohammad-Reza Ebadzadeh,[1,2] Simin-Dokht Habibzadeh,[2] Mohammad-Hassan Dehghani-Firouzabadi,[2] Abbas Etminan,[2] Faramarz Fazeli,[7] Maryamalsadat Mousavi[2,8]

[1]Physiology Research Centre, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Nephrology, Urology and Renal Transplantation, Afzalipoor Hospital, Kerman University of Medical Sciences, Kerman, Iran
[3]Gastroenterology and Hepatology Research Centre, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[4]Department of Pharmacology and Toxicology, School of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran
[5]Pharmaceutics Research Centre, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[6]Research Center for Hydatid Disease in Iran, Kerman University of Medical Sciences, Kerman, Iran
[7]Department of Urology, Zahedan University of Medical Sciences, Zahedan, Iran
[8]Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Introduction. Oxidative stress contributes to delayed graft function (DGF). Glutathione S-transferases (*GST*s) are polymorphic genes which produce enzymes with protective effect against oxidative stress. This study aimed to investigate the association between donors' and recipients' *GSTM1* and *GSTT1* polymorphisms and DGF, creatinine clearance, and oxidative stress parameters in kidney allograft recipients.

Materials and Methods. One hundred and eighty-two donor-recipient pairs were studied. Lipid peroxidation and total antioxidant capacity were measured in the recipients' plasma as the parameters of oxidative stress. Delayed graft function was determined based on at least 10% increase, no change, or less than 10% decrease in the serum creatinine level in 3 consecutive days during the 1st week after transplantation.

Results. Lipid peroxidation was significantly greater in the recipients with DGF ($P < .001$). The frequency of *GSTM1* null was significantly higher in the patients with DGF (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.17 to 0.86; $P = .02$). There was also a significant association between the donors' *GSTM1* polymorphism and DGF (OR, 0.31; 95% CI, 0.14 to 0.68; $P = .003$). A significant association was detected between combination of recipients and donors' *GSTM1* polymorphism and DGF (OR, 0.20; 95% CI, 0.07 to 0.64, $P = .006$). The recipients' *GSTM1* polymorphism, alone and in combination with donors' *GSTM1* and *GSTT1*, significantly affected the creatinine clearance on discharge day.

Conclusions. These results suggest that the donors and recipients' *GSTM1* polymorphism may be a major risk factor for oxidative stress and poor kidney allograft transplantation outcomes.

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INTRODUCTION

Delayed graft function (DGF) is a post-transplantation phenomenon which adversely influence the allograft functionality and survival. It is also shown that rejection episodes are more frequent in organs with DGF than it is in those that function immediately.[1-4]

Ischemic reperfusion injury (IRI) is a common

event in kidney transplantation, and it is considered as one of the main contributors to acute kidney injury and DGF in allografts.[3,5] In the ischemic phase, reduction of oxygen supply triggers production of reactive oxygen species (ROS) and an acidotic environment, which eventually result in phospholipolysis, endothelial membrane injury, and thrombin-mediated fibrin deposition.[3,5] In the reperfusion phase, these injuries are deteriorated by migration of inflammatory cells and reintroduction of oxygen into the damaged tissue. Excess oxygen plus activity of inflammatory cells lead to production of more ROS and thereby more intense damages to the cells and finally their apoptosis.

Among the numerous endogenous defence mechanisms against ROS and oxidative injury, glutathione plays a critical role in homeostasis of cellular redox environment.[6,7] Many studies have reported glutathione deficiency could intensify oxidative stress and IRI in different organs.[5,8-11] Glutathione S-transferases (GSTs) are a family of enzymes that catalyse the conjugation of the reduced glutathione thiolate anion with a wide range of electrophiles including ROS.[6] Glutathione S-transferases are highly polymorphic and these polymorphisms are likely to contribute to interindividual differences in response to oxidants. Recent studies emphasize the potentially distinctive roles of GST enzymes as crucial determinants of the development of IRI.[12]

To our knowledge, the role of GST polymorphisms in kidney allograft outcome has been reported in one study.[13] In this study, like the most related studies, only the role of donors' genetics in transplantation has been evaluated. Considering the crucial role of oxidative stress in the IRI, contribution of IRI to development of DGF after kidney allograft transplantation, and also the probable role of donors' genetics in transplantation, we hypothesized that *GSTM1* and *GSTT1* polymorphisms may partly explain individual variability in allograft function after transplantation. The aim of this study was to investigate the association between donors' and recipients' *GSTM1* and *GSTT1* polymorphisms and DGF, creatinine clearance, and oxidative stress parameters in kidney allograft recipients.

MATERIALS AND METHODS

Patients

One hundred and eighty-two recipient-donor pairs who had undergone kidney transplantation at 1 center (Afzalipour Hospital, Kerman, Iran) were enrolled in this prospective cohort study. The inclusion criteria for patients were grafting transplant from a living person, the first kidney transplant, and signing the consent form.

Delayed graft function was defined by stringent criteria on the basis of the Boom definition and independent from the need for dialysis,[2] as we reported in our previous articles.[14-16] According to this definition, an increase, no change, or a less than 10% decrease in the serum creatinine level in 3 consecutive days during the 1st week after transplantation was considered as DGF. Creatinine clearance was calculated using the Cockcroft-Gault formula, which in turn estimated glomerular filtration rate in mL/min.

Glutathione S-transferase M1 and T1 Genotyping

Genomic DNA was isolated from ethylenediaminetetraacetic acid whole blood using a rapid salting out DNA extraction method. After measuring the quality and quantity of the extracted DNA by determination of A_{260}/A_{280}, aliquots of the DNA were stored in Tris-ethylenediaminetetraacetic acid buffer at -70°C until the analysis of genotypes. According to our previous protocol,[17-19] a multiplex polymerase chain reaction (PCR) was performed to detect the null alleles of the *GSTM1* and *GSTT1* genes. The c-Abl gene was used as internal positive control. The primers used to amplify genotypes were 5′-GAA CTC CCT GAA AAG CTA AAG C-3′ and 5′-GTT GGG CTC AAA TAT ACG GTG G-3′ as forward and reverse primers, respectively, for the *GSTM1* (X68676.1, GeneBank), resulting in a 219-bp band, and 5′-TTC CTT ACT GGT CCT CAC ATC TC-3′ and 5′-TCA CCG GAT CAT GGC CAG CA-3′ as forward and reverse, respectively, for the *GSTT1* (AB057594.1, GeneBank) genotype, resulting in a 450-bp product. As internal control, the c-Abl gene was amplified using 5′-TTC AGC GGC CAG TAG CAT CTG ACT-3′ and 5′-TGT GAT TAT AGC CTA AGA CCC GGA GCT TTT-3′ as forward and reverse primers, respectively, producing a 750-bp product. The PCR reactions were resolved on 2% agarose gel electrophoresis and the PCR products were detected with ethidium bromide. The absence of the *GSTM1*- or *GSTT1*-specific fragments indicated the corresponding

null genotype, whereas the c-Abl specific fragment confirmed the presence of amplifiable DNA in the reaction mixture. The reliability and validity of the PCR method were assessed through reconducting the genotype assays using at least a 10% sample of our DNA samples. The results for all reassessments were 100% concordant.

Statistical Analysis

Continuous variables, including oxidative stress parameters, were compared using the unpaired *t* test according to the DGF occurrence and *GSTM1* and *GSTT1* polymorphisms. Individuals with at least 1 *GSTM1* and *GSTT1* active gene were coded 1 in analysis, and the second category included persons who were *GSTM1* and *GSTT1* null (coded zero). The logistic regression model was used to determine the association between the *GSTM1* and *GSTT1* polymorphisms and DGF in a univariable model. Odds ratios (ORs) and 95% confidence interval (CI) were used to estimate the risk of the association between DGF and a specific polymorphism. Backward regression analyses evaluated the independent predictors of the creatinine clearance at the discharge day. The association between the dependent variables (DGF and creatinine clearance at the day discharge) and the *GST* polymorphisms was adjusted using multivariable regression in the presence of potential confounders.[15,20] For all the tests, a *P* value less than .05 was considered significant. All the analyses were conducted using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Demographics, Clinical, and Laboratory Parameters

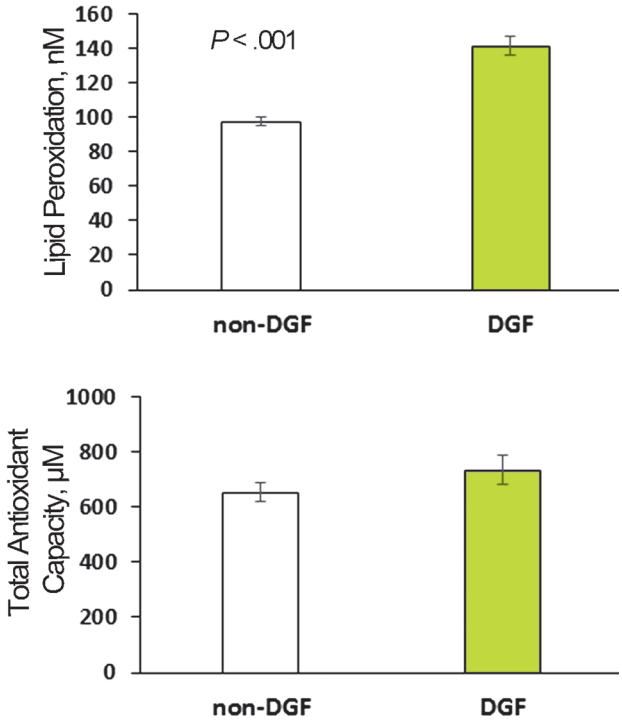
Eighty-two percent of the donors and 62% of the recipients were men (Table 1). The mean values of age for the donors and recipients were 28.6 ± 5.8 years and 40.7 ± 15.4 years old, respectively. Of all of the recipients, 11% and 20% suffered from acute rejection and DGF, respectively. Demographics of the recipients and donors according to their *GSTM1* and *GSTT1* polymorphisms are shown in Table 1.

Oxidative Stress Parameters and Delayed Graft Function

As it is shown in the Figure, the level of lipid peroxidation was significantly higher in the recipients who had DGF than those who had a normal functioning allograft.

Table 1. Donor, Recipient and Transplant Characteristics by *GSTM1* and *GSTT1* Polymorphisms

Parameter	Total	*GSTM1*			*GSTT1*		
		M1	Null	*P*	T1	Null	*P*
Donors							
Age, y	28.6 ± 0.4	27.9 ± 0.5	30.2 ± 0.7	.02	28.5 ± 0.6	28.7 ± 0.6	.86
Body mass index, kg/m^2	23.2 ± 0.3	23.2 ± 0.4	23.1 ± 0.7	.88	23.4 ± 0.5	22.4 ± 0.5	.25
Sex, n							
Male	149	103	46		104	45	
Female	33	33	10	.94	28	5	.08
Recipients							
Age, y	40.5 ± 1.1	40.1 ± 1.3	42.6 ± 2.3	.35	41.3 ± 1.3	38.5 ± 2.3	.28
Body mass index, kg/m^2	22.9 ± 0.4	22.9 ± 0.4	22.8 ± 0.7	.91	23.2 ± 0.5	22.2 ± 0.8	.29
Sex, n							
Male	112	86	26		81	31	
Female	61	45	17	.54	47	14	.49
Systolic blood pressure, mm Hg	158.6 ± 1.7	162.3 ± 1.9	148.9 ± 3.5	.001	160.2 ± 2.0	154.5 ± 3.5	.15
Diastolic blood pressure, mm Hg	95.9 ± 1.2	98.2 ± 1.8	92.5 ± 3.8	.13	95.9 ± 2.1	96.2 ± 3.6	.92
Mean arterial pressure, mm Hg	112.2 ± 1.2	116.3 ± 2.7	108.4 ± 3.6	.08	111.0 ± 2.8	113.4 ± 4.1	.61
Recipient diagnosis, %							
End-stage renal disease	55.3	48	56		59	50	
Diabetic nephropathy	10.6	8.3	11.4		8.9	7.7	
Hypertension	8.2	2.1	0.0		3.6	19.2	
Polycystic kidney	9.4	8.3	11.4		10.7	7.7	
Glomerulonephritis	12.9	16.7	8.6		14.3	11.5	
Others	3.6	16.6	12.6	…	13.5	13.9	…



Lipid peroxidation (LPO) and total antioxidant capacity (TAC) of allograft recipients and occurrence of DGF.

GSTM1 Polymorphism and Delayed Graft Function

The relationship between the donors and recipients' *GSTM1* polymorphisms and the incidence of DGF is shown in Table 2. The frequency of *GSTM1* null was significantly higher in the patients with DGF (OR, 0.38; 95% CI, 0.17 to 0.86; *P* = .02). There was also a significant association between the donors' *GSTM1* polymorphism and DGF events in the recipients (OR, 0.31; 95% CI, 0.14 to 0.68; *P* = .003). Considering the role of confounders in association between the *GSTM1* polymorphism and DGF,[20] multivariable logistic regression was performed in the presence of age, sex, body mass index, and mean arterial pressure variables. The adjusted association between the recipients' *GSTM1* polymorphism and DGF abolished in the presence of these confounders (OR, 0.37; 95% CI, 0.37 to 1.06; *P* = .06).

GSTT1 Polymorphism and Delayed Graft Function

The relationship between the donors and recipients' *GSTT1* polymorphisms and the incidence of DGF is shown in Table 3. The frequency of *GSTT1* null was not significantly different in the patients with and without DGF (OR, 1.67; 95% CI, 0.64 to 4.35; *P* = .29). There was also no significant association between the donors' *GSTT1* polymorphism and DGF events in the recipients (OR, 1.17; 95% CI, 0.48 to 2.80; *P* = .73). These associations remained insignificant in multivariable logistic regression in the presence of age, sex, body mass index, and mean arterial pressure variables.

Combination of Donors and Recipients' *GSTM1* Polymorphisms and Delayed Graft Function

Combinations of recipients and donors' *GSTM1* polymorphisms were analysed in order to determine if their interaction had a joint effect on DGF or not. There was a significant associations between combinations of recipient and donor *GSTM1* and DGF (OR, 0.20; 95% CI, 0.07 to 0.64, *P* = .006; Table 4).

Table 2. Association Between Kidney Allograft Donors and Recipients' *GSTM1* Polymorphism and Delayed Graft Function

GSTM1 Polymorphism	Delayed Graft Function		Unadjusted Analysis		Adjusted Analysis*	
	Yes	No	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Recipients	19 (59)	115 (79)	0.38 (0.17 to 0.86)	.02	0.37 (0.13 to 1.06)	.06
Donors	15 (47)	111 (74)	0.31 (0.14 to 0.68)	.003	0.17 (0.06 to 0.48)	.001

*Multivariable regression adjusted for age, sex, body mass index, and mean arterial pressure variables

Table 3. Association Between Kidney Allograft Donors and Recipients' *GSTT1* Polymorphism and Delayed Graft Function

GSTT1 Polymorphism	Delayed Graft Function		Unadjusted Analysis		Adjusted Analysis*	
	Yes	No	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Recipients	26 (72)	104 (72)	1.67 (0.64 to 4.35)	.29	0.92 (0.32 to 2.68)	.88
Donors	24 (75)	108 (74)	1.17 (0.48 to 2.80)	.73	1.67 (0.51 to 5.36)	.39

*Multivariable regression adjusted for age, sex, body mass index, and mean arterial pressure variables

Table 4. Association of Combination of Kidney Allograft Donors and Recipients' *GSTM1* Polymorphisms With Delayed Graft Function

GSTM1 Polymorphism	Delayed Graft Function		Unadjusted Analysis		Adjusted Analysis*	
	Yes	No	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Recipient null-donor null	7 (22)	13 (9)	1 (referent)	…	1 (referent)	…
Recipient null-donor M1	6 (19)	17 (12)	0.65 (0.18 to 2.42)	.53	0.14 (0.02 to 0.99)	.04
Recipient M1-donor null	9 (28)	25 (17)	0.67 (0.20 to 2.21)	.51	0.31 (0.60 to 1.46)	.14
Recipient M1-donor M1	10 (31)	90 (62)	0.20 (0.07 to 0.64)	.006	0.09 (0.02 to 0.40)	.002

*Multivariable regression adjusted for age, sex, body mass index, and mean arterial pressure variables

GSTM1 and *GSTT1* Polymorphisms and Oxidative Stress Parameters

The relationships between the donors and recipients' *GSTM1* and *GSTT1* polymorphisms and the levels of lipid peroxidation and total antioxidant capacity are shown in Table 5. There was a significant association between *GSTM1* polymorphism and lipid peroxidation as the level of lipid peroxidation was higher in the recipients with *GSTM1* null polymorphisms. Adjustment for the potential confounding factors did not change the associations.

GSTM1 and *GSTT1* Polymorphisms and Creatinine Clearance on Discharge Day

Changes in the creatinine clearance at the discharge is shown in Table 6. Among the polymorphisms, only the recipient *GSTM1* polymorphism correlated with creatinine clearance at discharge. This association was abolished when analysis was adjustment for the potential confounding factors.

DISCUSSION

The results of this study showed that lipid peroxidation was significantly higher in the allograft recipients who underwent DGF. There was also an association between both donors and recipients' *GSTM1* polymorphism and DGF as the frequency of DGF was significantly higher in the patients with *GSTM1* null allele or those who received allograft from *GSTM1*-null donors. Furthermore, linear regression demonstrated that lipid peroxidation in the allograft after transplantation was significantly linked to both donors and recipients' *GSTM1* polymorphism. There was no significant association

Table 5. Association Between Kidney Allograft Donors and Recipients' *GSTM1* and *GSTT1* Polymorphisms and Lipid Peroxidation and Total Antioxidant Capacity

Polymorphism	Lipid Peroxidation				Total Antioxidant Capacity			
	Unadjusted Analysis		Adjusted Analysis†		Unadjusted Analysis		Adjusted Analysis†	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Recipient *GSTM1*	-27 (-40 to -15)	< .001	-22 (-37 to -8.0)	.003	-53 (-197 to 91)	.46	-77 (-259 to 104)	.40
Recipient *GSTT1*	-3.2 (-16 to 9.6)	.61	-8.6 (-22 to 5)	.21	-161 (-301 to -22)	.02	-101 (-266 to 63)	.23
Donor *GSTM1*	-19 (-31 to -8)	.001	-22 (-34 to -9)	.001	-81 (-212 to 49)	.22	-94 (-252 to 63)	.24
Donor *GSTT1*	-13.3 (-25 to -1)	.03	-11 (-24 to 2)	.09	-53 (-189 to 82)	.44	-75 (-234 to 83)	.35

*CI indicates confidence interval.
†Multivariable regression adjusted for age, sex, body mass index, and mean arterial pressure variables.

Table 6. Association Between Kidney Allograft Donors and Recipients' *GSTM1* and *GSTT1* Polymorphisms and Creatinine Clearance*

Polymorphism	Creatinine Clearance			
	Unadjusted Analysis		Adjusted Analysis*	
	Coefficient (95% Confidence Interval)	*P*	Coefficient (95% Confidence Interval)	*P*
Recipient *GSTM1*	8.3 (0.6 to 15.9)	.03	8.3 (0.6 to 15.9)	.03
Recipient *GSTT1*	-0.5 (-8.8 to 7.8)	.91	-0.5 (-8.8 to 7.8)	.91
Donor *GSTM1*	4.1 (-3.6 to 11.7)	.28	4.1 (-3.6 to 11.7)	.28
Donor *GSTT1*	2.7 (-5.3 to 10.8)	.49	2.7 (-5.3 to 10.8)	.49

*Multivariable regression adjusted for age, sex, body mass index, and mean arterial pressure variables

between *GSTT1* polymorphism and DGF and oxidative stress parameters.

Evidence suggests that oxidative stress is a common mechanism of injury in acute and chronic rejections.[21-27] By altering the redox environment, ROS modulate the activation of transcription factors and cytokine genes involved in acute cellular rejection.[28-30]

The role of *GST* polymorphisms in the intensity of lipid peroxidation and kidney transplant outcome was also investigated by using both recipients and their donors. Frequency of *GSTM1* null polymorphism was higher in the recipients who had DGF and those who received allograft from the donors with *GSTM1* null genotype. There were also association between recipients' *GSTM1* and donors' *GSTM1* and lipid peroxidation. Glutathione S-transferases are a family of enzymes that protect the living system against electrophilic substances such as ROS through conjugating them with glutathione.[31] Although the effect of *GST* polymorphisms with oxidative stress and lipid peroxidation in kidney disease has been reported by several authors.[30,32,33] There are few studies regarding the association of *GST* polymorphisms and kidney allograft functions. Singh and colleagues[13] showed that patients with variant genotype of *GSTM1* and *GSTP1* were at a higher risk for rejection and DGF, respectively, supporting the hypothesis for involvement of GST isoform variants in allograft outcome in kidney transplant recipients. However, Azarpira and colleagues[34] reported no association between *GSTM1* and *GSTT1* gene polymorphisms and acute rejection. One interesting aspect of our findings was that the donors' *GSTM1* polymorphism was also involved in the allograft functions. In fact this finding which highlights the role of donors' genetics in transplantation has usually been overshadowed in most of the related studies.

Delayed graft function, as one of the main risk factors for acute rejection, is a multifactorial condition which is affected by the donor and recipient factors. The main factor for developing DGF is IRI of kidney allografts.[3,5,35] Free radicals including ROS are extensively generated in the early stage of reperfusion that cause allograft dysfunction during the first posttransplant week in various organs, including the liver,[36] brain,[37] heart,[35,38] and kidney.[39-41] Reactive oxygen species is known to trigger cytokine and chemokine cascades through nuclear factor-κB activation.[42] The transcription factor nuclear factor-κB is crucial in a series of cellular processes such as inflammation, immunity, cell proliferation and apoptosis.[42] Consistent with these findings, Danilovic and associates[43] showed that treatment of recipients with N-acetyl cysteine, as an antioxidant, could decrease DGF in recipients and made those recipients required fewer days of dialysis.

CONCLUSIONS

Our study demonstrated that donors and recipients' *GSTM1* polymorphism could determine the occurrence of DGF in kidney transplantation. Meanwhile, lipid peroxidation may play an important role in pathophysiology of DGF. Administration of antioxidants before kidney transplantation and considering both the donor and recipient polymorphisms of antioxidant genes can help to improve kidney allograft transplantation outcomes. Although the research has reached its aims, there are some avoidable limitations. Because of time limit, this research was conducted on a relatively small sample size. Meanwhile, there was no possibility for confirming the acute rejection by biopsy.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Ali Mandegary, PhD
Department of Pharmacology and Toxicology, School of Pharmacy, and Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Postal code: 7616911319, Iran
Tel: +98 34 3132 5011
E-mail: alimandegary@kmu.ac.ir

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