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A419C Polymorphism of Glyoxalase I Gene: Renal Function and Histological Findings at 12 Months after Renal Transplantation

Marie Jachymova[1], Irena Brabcova[2], Alexandra Germanova[1], Janka Slatinska[3], Oto Mestek[4], Ivo Matl[3], Tomas Zima[1], Ondrej Viklicky[2, 3], Marta Kalousova[1*]

[1]Institute of Clinical Chemistry and Laboratory Diagnostics, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic

[2]Transplant Laboratory, Transplant Center, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[3]Department of Nephrology, Transplant Center, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

[4]Institute of Chemical Technology, Prague, Czech Republic

Abstract

Background and Aims: AGEs (advanced glycation end products) are involved in the pathogenesis of vascular damage and progression of chronic kidney diseases. They are detoxified by the glyoxalase (GLO) system. The aim of the study was to test whether A419C polymorphism of GLO I gene is associated with the outcome of kidney transplantation.

Methods: A419C polymorphism of the GLO I gene was assessed in 145 renal transplant recipients and its relationship to histological changes in 12 months protocol kidney graft biopsy and renal function was examined.

Results: Genotype frequencies of the studied polymorphism corresponded to the expected frequencies according to Hardy-Weinberg equilibrium. No significant differences among allelic and genotype frequencies among patients with normal histological findings, interstitial fibrosis/tubular atrophy and subclinical rejection and renal parameters were found. However, a trend towards lower levels of serum creatinine and proteinuria was observed in patients with CC genotype.

Conclusions: This is the first study of glyoxalase I gene polymorphism in patients with the transplanted kidney. Although no significant relationship of the GLO I genotype to the histology of the transplanted kidney and renal parameters could be found, a trend towards better outcome in patients with the CC genotype was observed.

Keywords: Biopsy; Interstitial Fibrosis and Tubular Atrophy; Glyoxalase I; Kidney Transplantation; Polymorphism; Receptor for Advanced Glycation End Products

Introduction

Advanced glycation end products (AGEs) are formed via non-enzymatic glycation, which is enhanced during oxidative and carbonyl stress. This

*Correspondence:
Marta Kalousova, MD, PhD
Institute of Clinical Chemistry and Laboratory Diagnostics
1st Faculty of Medicine and General University Hospital, Charles University
Karlovo nam. 32, 121 11 Prague 2, Czech Republic
Tel: +420 224966620
Fax: +420 224962848
E-mail: marta.kalousova@seznam.cz, mkalousova@hotmail.com
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wide group of heterogeneous compounds is involved in the pathogenesis of chronic disease and their severe, often fatal complications, e.g. diabetes mellitus, vascular diseases, chronic renal failure and uremic complications and neurodegenerative diseases (Alzheimer´s disease) (1-4).

In patients with decreased renal function, serum advanced glycation end products are elevated several fold more than in patients with the normal renal function (5-7). Pentosidine and carboxy-methyllysine are markedly elevated in both plasma proteins and skin collagen of uremic patients. Thus, carbonyl stress as well as oxidative stress in uremia may contribute to the long-term complications associated with chronic renal failure and dialysis, such as dialysis-related amyloids and accelerated artherosclerosis (8).

The pathophysiological effect of AGEs could be diminished by their interaction with the soluble form of RAGE (receptor for AGEs) or by reducing AGE-precursors via specific reductases (3). Methylglyoxal and glyoxal, which are the major sources of intracellular and plasma AGEs, are metabolized predominantly by glutathione- and zinc dependent glyoxalase system (glyoxalases I and II) (9). The gene for glyoxalase I (GLO I) is located on chromosome 6 (locus 6p21,3 – 6p21,2), close to the major histocompatibility complex HLA-DR (10). It contains 6 exons, comprising 27,215 bp from the translation start site to the poly(A)site (11). Adenine/cytosine variation in the position 20 203 from the translation start site (exon 4) causes glutamic acid/alanine alteration in the position 111 in the protein sequence (12). The A419C polymorphism (also E111A or Glu111Ala polymorphism) has been studied in several AGE-related disorders yet, e.g. diabetes mellitus (13), Alzheimer´s disease (14) and in chronic hemodialysis patients in association with cardiovascular complications (15).

Vascular damage also plays a key role in the outcome of patients suffering from the end stage renal disease (ESRD) including kidney transplant recipients. In patients with biopsy-proven interstitial fibrosis and tubular atrophy (IF/TA), serum AGEs levels are higher in comparison to the renal transplant recipients with normal renal function and in patients with chronic renal failure of their native kidneys, indicating that increased AGEs level may be one of the factors among the non-immune mediators of IF/TA (16).

Although the role of AGEs in the vascular damage is generally accepted, no study has focused at glyoxalase I in patients with the transplanted kidney. The aim of the study was to find out whether there is any association of the polymorphism of the glyoxalase I gene with the clinical data and morphological changes in 12-months protocol kidney graft biopsy.

Materials and Methods

Study design and patients characteristics

The study was performed in the Institute of Clinical and Experimental Medicine in Prague, Czech Republic (sample collection in 2000-2001) and in the Institute of Clinical Chemistry and Laboratory Diagnostics of the First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic (genetic analysis in 2007-2008).

One hundred and forty-five Caucasian patients were included in this single center study. All of them had undergone kidney transplantation (TPL) in 2000-2001 and were treated with tacrolimus or cyclosporine A, mycophenolate mofetil and steroids-based immunosuppression. No antilymphocyte globulins´ induction immunosuppression was used.

Each patient underwent a biopsy of the kidney graft one year after TPL. At the time of the protocol biopsy, all patients were in stable clinical status without clinical and laboratory signs of acute infection (C - reactive protein less than 8 mg/l) and had no acute cardiac problems. All patients had stable

renal graft function without suspicion on acute rejection prior the biopsy. Only patients who underwent protocol biopsy and had adequate biopsy specimen were included in the study.

The demographic and clinical parameters as well as the basic clinical and laboratory characteristics of the studied patients one year after transplantation and renal parameters in each patients´ subgroup with different histological findings in the graft biopsy are provided inTables 1-3.

The study was approved by local Institutional Ethical Committee and all patients gave informed consent prior to entering the study.

Samples

Blood of the patients was collected via puncture of the arteriovenous fistule. Tubes with ethylene diamine tetraacetic acid were used for DNA analysis. Samples for routine biochemical and haematological analyses were collected as well.

Glyoxalase I polymorphism

The 203 bp long region containing Glu111Ala polymorphism was amplified by polymerase chain reaction (PCR) with primers, forward primer 5´GCA GGG GTT AGG CCA ATT AT3´ and reverse primer 5´CAG GCA AAC TTA CCG AAT CC3´,respectively. PCR proceeded with initial denature at 92 °C for five minutes, followed by 30 cycles of 94 °C for 30 seconds, 60 °C for 30 seconds and 72 °C for 1 minute, and additionally 68 °C for 5 minutes (Peltier ThermanCycler DNA Engine DYADTM, Bio-Rad, California, USA). For primers design, we used the Primer3 Input web application (http://frodo.wi.mit.edu/).

Restriction analysis was done with restriction endonuclease Bsm AI overnight at 37 °C. Fragments sizes were assessed using NebCutter V2.0 (http://tools.neb.com/NEBcutter2) as follows: 143bp and 60bp for wild-type allele 419A and 203bp for the mutant allele 419C. Finally, products were separated

Table 1. Demographic and clinical parameters of the study cohort at the time of transplantation

Parameter	Results
Number of patients (male/female)	145 (95/50)
Age (years)	47.5±13.1
Duration of dialysis treatment (days)	481 (260-1071)
PRA max (%)	4.0 (0-20.0)
HLA A, B, DR mismatch	2.9±1.3
Donor age (years)	45.0±15.0
Etiology of renal failure (number of patients)	
Glomerulonephritis	57
Interstitial nephritis	28
Polycystic kidney disease	28
Vascular nephrosclerosis	3
Diabetic nephropathy	10
Other	19

PRA max, maximal panel reactive antibodies.

Data are expressed as mean±SD (standard deviation), in case of high inter-individual variability as median (inter-quartile range).

Table 2. Basic clinical and laboratory characteristics of the studied patients 1 year after kidney transplantation

Parameter	Results
Number of patients (male/female)	145 (95/50)
Race – Caucasian (male/female)	145 (95/50)
BMI (kg/m²)	26.5±4.5
Blood pressure (systolic/diastolic, mmHg)	147±20 / 88±10
Acute rejection within the 1year after TPL	total number 63 in 43 patients
Creatinine (mmol/L)	147.0±89.4
GFR according to C-G formula (mL/s)	1.05±0.36
GFR according to MDRD formula (mL/s)	0.84±0.29
Proteinuria (g/day)	0.6±1.8
Cholesterol (mmol/L)	5.4±1.1
Triacylglycerols (mmol/L)	2.4±1.1
Blood glucose (mmol/L)	5.6±0.7
Graft biopsy finding (number of patients)	
Normal	70
Subclinical rejection	15
Chronic allograft nephropathy	60

BMI, body mass index; **C-G**, Cockcroft and Gault; **GFR**, glomerular filtration rate; **MDRD**, Modification of Diet in Renal Disease; **TPL**, transplantation

Data are expressed as mean±SD (standard deviation), in case of high inter-individual variability as median (inter-quartile range).

Table 3. Renal characteristics in each subgroup of transplanted patients with different histological findings in the graft biopsy

Parameter	Histology			P value
	Normal	SR	IF/TA	IF/TA vs. N
Number of patients (male/female)	70	15	60	
Creatinine (mmol/L)	126±39	128.6 (116-196)	154±44	p=0.00011
GFR according to C-G formula (mL/s)	1.13±0.37	0.99±0.42	0.98±0.32	p=0.0093
GFR according to MDRD formula (mL/s)	0.92±0.29	0.79±0.34	0.76±0.24	p=0.00034
Proteinuria (g/day)	0.3±0.5	0.5±0.8	0.8±2.8	p=0.048

IF/TA, interstitial fibrosis and tubular atrophy; **C-G**, Cockcroft and Gault; **GFR**, glomerular filtration rate; **MDRD**, Modification of Diet in Renal Disease; **N**, normal; **SR**, subclinical rejection.

Data are expressed as mean ± SD (standard deviation), in case of high inter-individual variability as median (inter-quartile range). Significance was calculated with Wilcoxon test.

by electrophoresis in 3% agarose gel and visualized in UV light (Transilluminator TS-312A Spectroline®, New York, USA) after ethidium bromide staining.

Other laboratory parameters

Routine clinical chemistry methods were used for serum and urine analysis. Creatinine in serum was assessed with Jaffé reaction, glucose was determined with glucose oxidase and peroxidase method and protein in urine was measured with pyrogallol red. The values of cholesterol level were acquired with cholesterol-oxidase and peroxidise methods, triacylglycerols levels with glycerolphosphate oxidase and peroxidase method.

Graft function was evaluated using calculation of glomerular filtration rate according to Cockcroft and Gault (17) and abbreviated MDRD (modification of diet in renal disease) formula (18).

All biopsies were done by a 14G tru-cut needle (Uni-Cut Nadeln, Angiomed) guided by ultrasound (Toshiba, Power Vision 6000). The renal tissue taken by core biopsy was used for routine histology performed by the standard method. Tissues were fixed in 10% formalin for 15-30 min and then processed in TPC 15 tissue processor (MEDITE Histotechnik, Germany). Four μm thick paraffin embedded tissue sections were stained with hematoxylin and eosin, periodic acid-Schiff, aldehyde-fuchsin orange G, Sirius red with elastic stain and periodic acid silver-methenamine. Biopsy tissues were scored on the basis of the Banff 07 working classification (19). Subclinical rejection was defined as an acute rejection finding in protocol biopsy in patients with stable graft function.

Statistics

The results of biochemical parameters are expressed as mean ± standard deviation, in an exceptional case of high inter-individual variability as median (interquartile range). Comparison of continuous variables was performed with one-way ANOVA (analysis of variance) or the Kruskal-Wallis test, and unpaired t-test or Wilcoxon test, as appropriate. $\chi 2$ or Fisher´s exact test were used for comparison of proportions and for testing of Hardy Weinberg equilibrium. Associations between parameters were assessed using Pearson and Spearman correlation coefficients, according to the data distribution. Haplotype analysis was used for more detailed description. The tests used were two-sided and all results were considered as statistically significant at $p<0.05$.

Results

Genotype frequencies of the studied polymorphism corresponded to the expected frequencies according to Hardy-Weinberg equilibrium. A allele was found in 47.1% of patients with normal histology, in 50.0% of patients with subclinical rejection and in 51.7% of IF/TA patients. Allelic as well as genotype frequencies did not differ between subgroups of transplanted patients with different histological findings in the graft biopsy; however, a tendency to lower prevalence of the CC genotype could be observed in the IF/TA subgroup compared to the subgroup with normal histological findings (Table 4).

Table 4. Allelic and genotype frequencies of A419C polymorphism of the glyoxalase I (GLO1) gene in each subgroup of transplanted patients with different histological findings in the graft biopsy

Allelic frequencies (%)	Normal	SR	IF/TA
A	47.1	50.0	51.7
C	52.9	50.0	48.3
Genotype frequencies (%)			
AA	22.9	20.0	22.0
AC	48.5	60.0	59.4
CC	28.6	20.0	18.6

IF/TA, interstitial fibrosis and tubular atrophy; **SR**, subclinical rejection

There was no correlation between A419C polymorphism of GLO I gene and the severity of IF/TA when separated to grade I-III.

Concerning association of genotypes with the renal parameters, multiple comparison with ANOVA and Kruskal-Wallis test did not show any relationship of the genotype to the graft function and proteinuria. However, with paired comparison with Wilcoxon or Student t-test, a trend to lower levels of serum creatinine and proteinuria was observed in patients with CC genotype (Table 5).

Statistical evaluation with ANOVA and Kruskal-Wallis test were not significant. Paired comparison performed with Wilcoxon or Student t-test.

Table 5. Renal characteristics in each subgroup of transplanted patients with different genotype findings in the graft biopsy

Parameter	Genotype			P value
	AA	AC	CC	
Number of patients	33	78	34	
GFR according to C-G formula (mL/s)	0.992±0.345	1.04±0.368	1.13±0.352	
GFR according to MDRD formula (mL/s)	0.809±0.250	0.824±0.304	0.913±0.268	p=0.038*
Creatinine (mmol/L)	143±48.6	158±114	126±36.7	
Proteinuria (g/day)	0.636±1.27	0.711±2.36	0.229±0.204	p=0.012 § p=0.032†

C-G, Cockcroft and Gault; **GFR**, glomerular filtration rate; **MDRD**, Modification of Diet in Renal DiseaseData are expressed as mean±SD (standard deviation), in case of high inter-individual variability as median (inter-quartile range).
*Cc Vs Ac §Cc Vs Aa †Cc Vs Ac

Discussion

This is the first study dealing with polymorphism of the glyoxalase I gene in patients with the transplanted kidney. Although no significant relationship of the GLO I genotype to histology of the transplanted kidney and renal parameters could be found, a trend to better outcome in patients with the CC genotype was observed.

AGEs are wide group of heterogeneous compounds, which are able to modify biological macromolecules and change their physical and chemical characteristics and their metabolism. The glycation of DNA via AGEs gives rise to characteristic nucleotide adducts, that are associated with mutagenesis and carcinogenesis (20). Intracellular accumulation of advanced glycation end products is involved also in abnormal cross-linking formation, importantly at collagen level, which is very relevant mechanism of AGEs damage (21).

Interstitial fibrosis and tubular atrophy is characterized by a relatively slow but variable rate of decline in renal function after the initial three post-transplant months (22), often in combination with artherosclerosis, glomerular lesions, tubular atrophy and internal fibrosis (23). Involvement of AGEs in IF/TA is supported by several studies. Raj et al (16) found increased serum AGEs levels in patients with biopsy-proven IF/TA in comparison to renal transplant recipients with normal renal function and patients with chronic renal failure of their native kidneys and suggested that increased AGEs level may

be one among the nonimmune mediators of IF/TA. Renal accumulation of AGEs occurs in allograft rat model of experimental IF/TA (24). Renal deposition of the AGE pentosidine in proximal tubular cells is increased in renal transplant recipients, which is related to increased serum levels of pentosidine (25). Finally, accumulation of AGEs in the skin is associated with IF/TA (26).

The effect of AGEs on the cells is also mediated indirectly via interaction with their specific receptor RAGE. Soluble form of RAGE (sRAGE), primarily found in blood, is a naturally occurring inhibitor of pathological effect mediated via RAGE (27). AGE-RAGE interaction results in the activation of signal transduction pathway of nuclear factor κB (NF-κB). NF-κB stimulates transcription of genes for cytokines and growth factors, adhesion molecules, stimulation of cell proliferation, increase of vascular permeability, induction of migration of macrophages (28, 29). Our studies demonstrated elevation of sRAGE in dialysis patients (27, 30), its decrease after renal transplantation and correlation with the early chronic vascular changes in the transplanted kidney (31). Higher levels of sRAGE were observed in chronic hemodialysis patients with CC genotype (15). Low levels of sRAGE are associated with increased risk for mortality in renal transplant recipients as well (32).

The main function of glyoxalase I is to decrease concentration of reactive intermediates of glycolysis, precursors of AGEs. Decreased glyoxalase I activity due to the aging process and oxidative stress, results in increased glycation and tissue damage (33). Low-molecular AGEs (34) as well as carboxymethyllysine, one of the AGE-products (35), were described as predictors of mortality in patients on chronic hemodialysis.

The importance of glyoxalase I has been investigated in pathogenesis of diabetes mellitus and its complications, chronic renal failure and uremia, the states related to accumulation of AGEs (13, 36). Moreover, glyoxalase I was studied in several human malignancies, such as in colon tumor tissue (37), neoplastic lung tissue (38) and in tumor urogenital tissue (39).

Till now, no other study except ours has focused at A419C polymorphism of GLOI gene in transplanted patients. We did not find any significant relationship of the genotype to the graft function and proteinuria. Only a trend to better outcome in patients with the CC genotype was observed. We obtained similar negative results from our previous study of the RAGE polymorphisms (-429T/C, -374T/A, Gly82Ser, 2184A/G), which involved the same group of transplanted patients (40).

Although a trend of better prognosis in transplanted patients with the CC genotype was observed, in our previous study in chronic hemodialysis patients, we described an association of CC genotype of glyoxalase I polymorphism with vascular complications in hemodialysis patients (15). Additionally, we found an association of the C allele with the worse prognosis in patients with breast cancer (41). A419C polymorphism was studied in association with Alzheimer's disease (14) as well, however, no relationship with to the disease was observed. Junaid et al suggest, that the homozygosity for A419 resulting in Glu111 is a predisposing factor of autism (42). Another study of glyoxalase I gene frequencies has shown that there is a significant excess of glyoxalase homozygote GLO 1-1 (homozygote CC) and a deficiency of types GLO 2-1 (heterozygote AC) and GLO 2-2 (homozygote AA) in insulin-dependent diabetic patients (13). Further studies with much higher number of patients would be required to clarify the impact of the mutated allele on the diseases, where AGEs are involved in the pathogenesis.

Our study is limited by the relatively small number of patients. Our results do not exclude possible associations of GLO I gene polymorphisms with extreme phenotypes such as graft failure soon after transplantation. These patients were not studied as there was

no reason to perform protocol biopsy 1 year after transplantation and the study is based on histological findings. Additionally, small number of patients with diabetic nephropathy in our study population did not enable us to look at the association with diabetes. There are surely other factors contributing to the better outcome of transplanted patients than only genetic ones. Further evaluation of this problem would require more profoundly expressed differences among subgroups and also higher number of subjects would be a great advantage.

Conclusions

In conclusion, this is the first study dealing with polymorphism of the glyoxalase I gene in patients with the transplanted kidney. Although no significant relationship of the GLO I genotype to histology of the transplanted kidney and renal parameters was found, a trend towards better outcome in patients with the CC genotype was observed.

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Conflict of Interest

None declared.

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