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Original Paper

Association Between GLCCI1 Promoter Polymorphism (Rs37972) and Post-Transplant Hypertension in Renal Transplant Recipients

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Key Words
Glcci1 • Polymorphism • Transplantation • Post-transplant hypertension

Abstract
Background/Aims: Post-transplant hypertension is highly prevalent in renal transplant recipients and is a risk factor for graft loss, cardiovascular disease and death. Glucocorticoid is used to prevent rejection, but simultaneously increases the risk of post-transplant hypertension. The glucocorticoid-induced transcript 1 (*GLCCI1*) promoter polymorphism (rs37972) has been reported to be associated with response to glucocorticoid therapy in asthma. We therefore examined the association between *GLCCI1* promoter polymorphism and post-transplant hypertension in renal transplant recipients. ***Methods:*** We conducted a retrospective cohort study of renal transplantation at a single university hospital from October 2003 to January 2014. Fifty consecutive adult recipients were analyzed, with clinical data retrieved from a prospectively collected database. Genotyping was carried out using genomic DNA derived from recipient's blood. GLCCI1 immunoreactivity in vascular endothelial cells was quantitatively analyzed by immunohistochemical staining of recipients' native kidney biopsy-specimens. The primary outcome measure was post-transplant hypertension. ***Results:*** Post-transplant hypertension was observed in 14/17 (82%) of recipients with CC, 18/20 (90%) with CT, and 2/13 (15%) with TT genotype. CC/CT genotype was significantly associated with post-transplant hypertension, even after adjustment for covariates (odds ratio, 10.6; 95% confidence intervals, 1.32 to 85.8; P = 0.026). In addition, we observed that GLCCI1 immunoreactivity in

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arteriolar endothelial cells was higher in kidney specimens obtained from recipients with a CC/CT genotype than a TT genotype (P = 0.021). ***Conclusion:*** GLCCI1 promoter polymorphism rs37972 may be associated with post-transplant hypertension.

Introduction

Hypertension is prevalent not only in patients with advanced chronic kidney disease (CKD) or end stage renal disease (ESRD), but also in renal transplant recipients. This post-transplant hypertension is a risk factor for graft loss, cardiovascular disease and death [1-4]. Moreover, post-transplant hypertension is reported to occur in 40 to 80% of cases [5-7] and is attributed to multiple factors, namely, older age, increased body mass index (BMI), reduced allograft function, acute and chronic rejection, high sodium intake, history of hypertension, and prior administration of immunosuppressive drugs (e.g. calcineurin inhibitor (CNI), cyclosporine, tacrolimus, or glucocorticoids) [6, 8]. The mechanism of glucocorticoid-induced hypertension is known to involve the inhibition of vasodilation [9-14]. However, it remains unknown what types of patients develop post-transplant hypertension in response to glucocorticoid usage and what types do not.

The glucocorticoid-induced transcript 1 (*GLCCI1*) gene is considered to be associated with glucocorticoid sensitivity [15]. Recently, a single-nucleotide polymorphism (SNP; rs37972) located within the promoter region of the *GLCCI1* gene has been shown to contribute to glucocorticoid sensitivity in patients with asthma, through a genome-wide association study (GWAS) [16]. However, the association of this *GLCCI1* promoter polymorphism with post-transplant hypertension has not been previously evaluated. In this study, we therefore examined the relationship between *GLCCI1* promoter polymorphism, GLCCI1 immunoreactivity, and post-transplant hypertension, in a retrospective analysis of renal transplant recipients.

Materials and Methods

Patients

We conducted a retrospective cohort study of patients treated with renal transplantation at a single university hospital from October 29, 2003, through to January 30, 2014. A total of 52 consecutive adult patients who received a primary renal transplantation from a living related donor were eligible for the study. Key exclusion criteria comprised those patients receiving transplantation from an unrelated donor, those whose treatment was not based on an immunosuppressive regimen (described below), those who had previously received renal transplantation and/or a transplant of any other organ, and those who underwent steroid withdrawal. A total of two patients were excluded, comprising one who had received renal transplantation from a living unrelated donor, and one patient that was not placed on an immunosuppressive regimen, resulting in a total of 50 patients for analysis. This study protocol was reviewed and approved by ethical committee of Jikei University School of Medicine (approval #26-110 7615), as well as by the institutional review board at Jikei University Hospital. All the patients provided their written, informed consent to participate, and the study was conducted in full compliance with the principles of the Declaration of Helsinki.

Immunosuppressive regimens

All recipients received induction-immunosuppressive treatment. 500 mg of methylprednisolone (MP) was given on day 0, and 20 mg of basiliximab was given on days 0 and 4. Other immunosuppressive drugs (CNI and mycophenolate mofetil) were given at the same daily doses, and on the same schedule, as in the induction and maintenance phases. MP (0.3 mg/kg/day) was also given two days prior to transplantation, then reduced by 4 mg each week to reach a maintenance dose by week 5, and then continued at 4 mg/day post-transplantation.

Patient Data and Follow-up

Clinical data were collected from the electronic clinical database and patient's medical records. Estimated glomerular filtration rates (eGFR) (mL/min/1.73 m^2) were calculated using the Japanese eGFR equation [17]. 24-hour urine protein and sodium excretion were quantified using urine samples [18]. Biopsy-proven acute or chronic rejection was diagnosed on kidney biopsy, according to the Banff 2013 classification [19].

Outcomes

The primary outcome was post-transplant hypertension at 3 years, defined as: (1) patients with blood pressure greater than 130/80 mmHg on multiple occasions; or (2) those taking antihypertensive medications prescribed according to the *Kidney Disease: Improving Global Outcomes Clinical Practice Guideline* [20].

Genotyping

We collected 8 mL of peripheral blood from each recipient in tubes containing potassium-EDTA. Genomic DNA was extracted from leukocytes using a Genomic DNA extraction kit (Biologica, Nagoya, Japan) by SRL Inc. (SRL, Tokyo, Japan). To determine the *GLCCI1* genotype for SNP rs37972, genomic DNA was amplified by polymerase chain reaction with newly designed primers (PCR; forward primer, 5'–CTTTCTCGTCTGAACACACAAG-3'; reverse primer, 5'- CGAAGCAGATAGCTTCTTGG -3') and then sequenced. Both PCR and direct sequencing were performed as described previously [21].

Immunohistochemical staining

Eight native kidney-specimens, retrospectively collected from recipients, were assessed. These kidney-specimens were stained with anti-GLCCI1 antibody (rabbit primary antibody (pAB), 1:50; Abcam, Cambridge, UK; catalog ab171137), and anti-CD34 antibody, used as specific endothelial marker (rabbit pAB, 1:500; Abcam, Cambridge, UK; catalog ab81289). Immunohistochemical staining was performed as described previously [22]. Reaction products were visualized by staining with 3, 3-diaminobenzidine tetrahydrochloride, before counter-staining sections with Periodic-Acid-Schiff. Negative controls were performed by omitting pABs. Since GLCCI1 immunoreactivity is strong in lymphocytes, these were used as positive controls for GLCCI1 expression [16].

Morphometric analysis

Previous publications have defined arterioles as being blood vessels with an inside diameter < 100 μm [23], however blood vessels are continuous and the arterioles are not clearly defined [24]. In this study, we defined arterioles as being blood vessels with an inside diameter < 100 μm and with one to four layers of smooth muscle cells [25-27]. GLCCI1 immunoreactivity was defined as the ratio of GLCCI1 to CD34 positive endothelial cells counted in the arterioles of each whole biopsy specimen, expressed as a percentage. Staining was evaluated under light microscope (Olympus BX51: Olympus, Tokyo, Japan), and all scoring was performed blinded to clinical information and genotype.

Statistics

Patient characteristics were stratified by *GLCCI1* genotype and compared with the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. Differences in normalized GLCCI1 immunoreactivity (i.e. the GLCCI1/CD34 ratio) between different genotypes were compared using the Mann-Whitney test. In analyses of post-transplant hypertension, logistic regression analysis was used to calculate each odds ratio (OR) with a 95% confidence interval (95% CI). Risk factors for post-transplant hypertension were examined with the use of univariate and multivariate logistic regression; factors with a P value of less than 0.05 in univariate analysis were included in multivariate analysis. All statistical analyses were performed using STATA 14.0 (STATA Crop., College Station, TX), with $P<0.05$ being considered statistically different in all tests.

Results

Baseline Characteristics

A total of 50 consecutive renal transplant recipients were analyzed in this study. The frequency of *GLCCI1* genotypes in this cohort (CC 34%, CT 40%, and TT 26%) was in agreement with the genotype frequency recorded in the HapMap database [28]. Table 1 summarizes the baseline characteristics of these recipients stratified by *GLCCI1* genotype; there were no significant differences in these clinical features other than for age.

Association between GLCCI1 promoter genotype and antihypertensive medication

Although use of antihypertensive drugs was not significantly different among GLCCl1 genotypes prior to transplantation (Table 1), there was a significant difference at 3-years post-transplantation (Table 2). Antihypertensive drugs were used more often in recipients with CC (65%) or CT (85%) genotypes than in those with a TT (15%) genotype (P < 0.001). Similarly, ACE-I or ARB drugs were used more often in those with CC (65%) or CT (65%) genotypes than in those with a TT (15%) genotype (P = 0.009). Calcium-channel blockers (CCBs) were also used more often in those with CC (53%) or CT (60%) genotypes, than in those with a TT (15%) genotype (P = 0.033). There were no significant differences in blood pressure, kidney function, other drug use, or rejection episodes in regard to *GLCCI1* genotype.

Association between GLCCI1 promoter genotype and post-transplant hypertension

Post-transplant hypertension was observed in 14/17 (82%) of recipients with a CC genotype, 18/20 (90%) with a CT genotype, and 2/13 (15%) with a TT genotype. Univariate logistic regression analysis demonstrated that donor hypertension (P = 0.004) and recipient CC/CT genotype (P < 0.001) were significantly associated with post-transplant hypertension (Table 3). Subsequent multivariate logistic regression was performed, adjusting for the association of age with *GLCCl1* genotype, and the association of donor hypertension with post-transplant hypertension. Even after adjustment for these two factors, a CC/CT genotype remained a significant risk factor for post-transplant hypertension (Table 3; OR, 10.6; 95% CI, 1.32 to 85.8; P = 0.026).

Table 1. Baseline characteristics of study recipients stratified by GLCCI1 genotype. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CGN, chronic glomerulonephritis; DM, diabetes mellitus. *Kruskal-Wallis test. Data are shown as median with 25-75 percentiles. †Chi square test

	Total	CC	CT	TT	P value
No. patients (%)	50 (100%)	17 (34%)	20 (40%)	13 (26%)	
Median age (year)	35 (29 – 45)	35 (29 – 40)	39 (33 – 54)	30 (27 – 42)	0.046*
Male, n (%)	34 (68)	12 (71)	16 (80)	6 (46)	0.12†
Body mass index (kg/m^2)	21 (19-24)	20 (19-22)	23 (21-24)	19 (18-22)	0.063*
Duration of dialysis (month)	22 (11 – 52)	22 (10 – 64)	26 (13 – 43)	13 (9 – 52)	0.74*
Donor type, n (%)					
Living related	50 (100)	17 (100)	20 (100)	13 (100)	-
Blood pressure (mmHg)					
Systolic	140 (130-150)	136 (130-150)	140 (130-154)	141 (130-143)	0.65*
Diastolic	82 (73-90)	82 (72-90)	86 (80-94)	76 (64-84)	0.14*
Drug use before transplantation, n (%)					
Antihypertensive drugs	32 (64)	10 (59)	15 (75)	7 (54)	0.40†
ACE-I or ARB	22 (44)	5 (29)	11 (55)	6 (46)	0.29†
CCB	21 (42)	6 (35)	10 (50)	5 (38)	0.64†
Alpha-blocker	12 (24)	3 (18)	5 (25)	4 (31)	0.70†
Beta-blocker	8 (16)	2 (12)	3 (15)	3 (23)	0.70†
Diuretics	18 (36)	5 (29)	8 (40)	5 (38)	0.78†
The number of antihypertensive drugs	1 (0-3)	1 (0-2)	2 (0-3)	2 (0-3)	0.58†
Primary disease, n (%)					0.48†
CGN	33 (66)	9 (53)	14 (70)	10 (77)	
Hypertension	4 (8)	1 (6)	2 (10)	1 (7)	
DM	2 (4)	2 (12)	0 (0)	0 (0)	
Other	11 (22)	5 (29)	4 (20)	2 (15)	

Table 2. Clinical data at 3-years post-transplantation for recipients stratified by GLCCI1 genotype. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, Calcium channel blocker; eGFR, estimated glomerular filtration rate. *Kruskal-Wallis test. Data are shown as median with 25-75 percentiles. †Chi square test

No. patients (%)	Total 50 (100%)	CC 17 (34%)	CT 20 (40%)	TT 13 (26%)	P value
Blood pressure (mmHg)					
Systolic	123 (117-129)	124 (112-130)	124 (118-130)	120 (114-126)	0.63*
Diastolic	78 (74-83)	78 (76-80)	82 (74-86)	76 (68-80)	0.25*
eGFR (ml/min/1.73m^2)	50 (43-55)	51 (43-56)	45 (39-56)	50 (45-53)	0.41*
Urine Protein (mg/day)	59 (17-134)	17 (0-99)	76 (39-159)	65 (38-133)	0.25*
Drug use at 3 years, n (%)					
Statin	11 (22)	2 (12)	6 (30)	3 (23)	0.41†
Antidiabetic drugs	2 (4)	2 (12)	0 (0)	0 (0)	0.12†
Antihypertensive drugs	30 (60)	11 (65)	17 (85)	2 (15)	<0.001†
ACE-I or ARB	26 (52)	11 (65)	13 (65)	2 (15)	0.009†
CCB	23 (46)	9 (53)	12 (60)	2 (15)	0.033†
Alpha-blocker	2 (4)	1 (6)	1 (5)	0 (0)	0.69†
Beta-blocker	5 (10)	1 (6)	4 (20)	0 (0)	0.14†
Diuretics	0 (0)	0 (0)	0 (0)	0 (0)	-
The number of antihypertensive drugs	1 (1-2)	2 (1-2)	1 (1-3)	0 (0-1)	0.055†
Clinical course until 3-years, n (%)					
Acute/Chronic Rejection	6 (12)	1 (6)	3 (15)	2 (15)	0.63†

Table 3. Univariate and multivariate logistic regression analyses - association between post-transplant hypertension and covariates. * Estimated dietary salt intake by urinary sodium excretion; † Covariate confirmed by renal biopsy until 3-years post-transplantation; ‡Reference; OR, Odds Ratio

Covariate	Univariate logistic regression			Multivariate logistic regression		
	OR	p-value	95% CI	OR	p-value	95% CI
Age	1.01	0.73	0.96-1.05	0.96	0.43	0.88-1.05
BMI	1.12	0.19	0.94-1.34			
eGFR	1.00	0.92	0.95-1.04			
Rejection†	1.55	0.55	0.37-6.47			
Daily sodium intake*	1.25	0.12	0.95-1.66			
Donor hypertension	11	0.004	2.16-55.9	3.37	0.18	0.57-20.0
rs37972 CC and CT genotypes	35.2	<0.001	5.95-208	10.6	0.026	1.32-85.8
rs37972 TT genotype	1‡			1‡		

To confirm that these observations were robust, we also analyzed the association between *GLCCI1* C allele or T allele at rs37972 and post-transplant hypertension. The C and T allele frequency in recipients with post-transplant hypertension was 85% and 48%, respectively (OR, 1.77; 95% CI, 1.42 to 2.20; P<0.0001).

Evaluation of GLCCI1 immunoreactivity in vascular endothelial cells

Next, we examined *GLCCI1* immunoreactivity in vascular endothelial cells using immunohistochemical staining of native kidney-specimens from recipients (Fig. 1). In recipients with a CC/CT genotype, we observed strong GLCCI1 staining in the nucleus and moderate staining in the cytoplasm of arteriolar endothelial cells. In contrast, weak GLCCI1 staining was observed in those with a TT genotype. Mean GLCCI1 immunoreactivity in arteriolar endothelial cells was 26 to 44% in those with a TT genotype and 50 to 82% in those with a CC/CT genotype (Table 4). Normalized GLCCI1 expression in arteriolar endothelial cells was higher in those with a CC/CT genotype, compared to those with a TT genotype (P = 0.021; Mann-Whitney test).

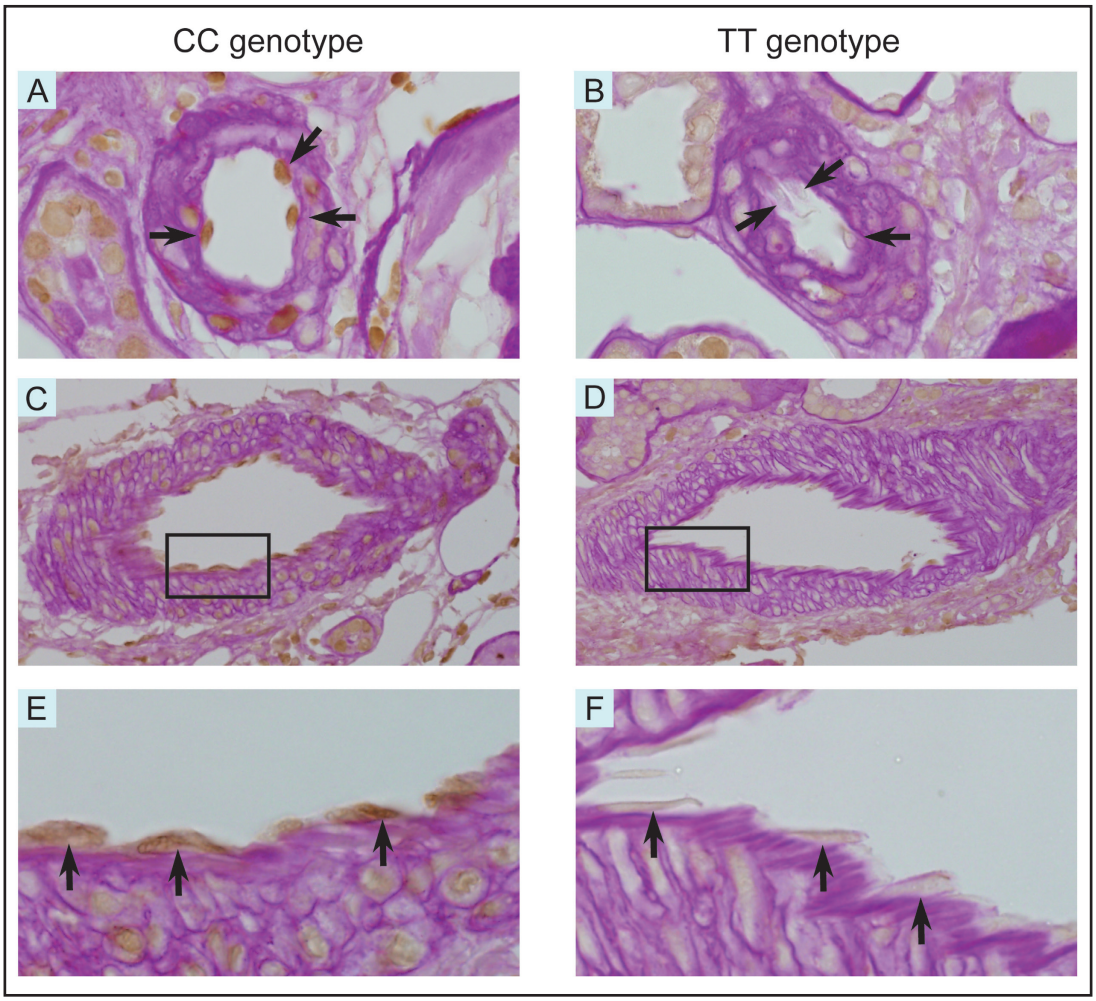

Fig. 1. GLCCI1 immunoreactivity in arteriolar vascular endothelial cells. Arterioles with an inside diameter of 30 μm in kidney-specimens obtained from CC genotype (A) and TT genotype (B) transplant recipients. Arterioles with an inside diameter of 90 μm in kidney-specimens obtained from CC genotype (C, E) and TT genotype (D, F) recipients. In all panels, brown staining shows positivity for the GLCCI1 antigen.

Table 4. Pathological data of GLCCI1 immunoreactivity in arteriolar vascular endothelial cells of recipients. * No. of arterioles in recipient's biopsy specimen. †GLCCI1 immunoreactivity was defined as the ratio of GLCCI1 to CD34 positive endothelial cells counted in the arterioles of each biopsy specimen, expressed as a percentage. Then mean of GLCCI1 immunoreactivity was calculated. Plus-minus values are means ± SD

Patients No.	GLCCI1 genotype	No. of arterioles*	Mean of GLCCI1 immunoreactivity in endothelial cells† (%)
1	TT	8	25.9 ± 0.2
2	TT	19	44.1 ± 0.3
3	TT	30	41.1 ± 0.3
4	TT	8	40.0 ± 0.2
5	CC	14	59.9 ± 0.3
6	CT	6	46.7 ± 0.4
7	CT	5	82 ± 0.2
8	CC	17	70.8 ± 0.2

Discussion

In this study, we found that transplant recipients with a *GLCCI1* promoter TT polymorphism had significantly less post-transplant hypertension, even after adjustment for covariates. We also examined GLCCI1 immunoreactivity in the vascular endothelial cells of recipients. From these results, it is speculated that GLCCI1 promoter polymorphism may be associated with post-transplant hypertension through altered GLCCI1 immunoreactivity in the arteriolar endothelial cells of recipients and glucocorticoids may increase blood pressure by direct stimulation of these cells.

Several groups have reported an association between SNPs that contributes to the variability of glucocorticoid sensitivity and blood pressure responses (e.g. the serum/glucocorticoid regulated kinase 1 gene SNP rs9376026 [29], and the glucocorticoid receptor gene SNP rs6198 [30]). However, an association between GLCCI1 polymorphism and blood pressure responses has not previously been reported.

The *GLCCI1* rs37972 TT genotype has previously been shown to be associated with a poorer response to treatment with inhaled glucocorticoids than the CC genotype in Caucasians [16]. The authors of that study also examined allelic differences in promoter activity in lymphoblastoid B cells using luciferase. Lymphoblastoid B cells with a TT genotype were found to have significantly lower expression of GLCCI1 than those with a CC genotype. Another group has reported that the TT genotype is associated with higher asthma severity than the CC genotype in Asians [31], and measured GLCCI1 expression in the bronchial epithelial cells of asthmatic patients. Staining intensity was not found to be significantly different between the two genotypes in that study; however, the amount of GLCCI1 protein produced in cultured epithelial cells in the presence of a corticosteroid was less for those with a TT genotype than for those with a CC genotype. Such associations are thus well recognized in the field of respiratory medicine. In contrast, there is little known about the association of GLCCI1 genotypes and steroid sensitivity in the field of nephrology. One group has previously examined pediatric patients with nephrotic syndrome, however GLCCI1 genotypes were not found to be associated with steroid sensitivity [32]. In the present study, we therefore examined the relationship between *GLCCI1* promoter polymorphism, GLCCI1 immunoreactivity, and post-transplant hypertension in adult transplant recipients. Our study shows that recipients with a TT genotype have less post-transplant hypertension and are prescribed fewer anti-hypertensive drugs. These findings suggest that a TT genotype in the *GLCCI1* promoter region may be associated with a reduction in promoter activity and GLCCI1 immunoreactivity. TT genotype recipients are thus less sensitive to glucocorticoids, and are less prone to elevations in blood pressure as a side effect of this medication. Arguing against this hypothesis however, is the fact that rates of rejection were not statistically significant between genotypes.

Interestingly, we found that GLCCI1 immunoreactivity was observed not only in vascular endothelial cells, but also vascular smooth muscle cells and renal tubular epithelial cells. In regard to the latter, there was a characteristic distribution of GLCCI1 immunoreactivity, being stronger in epithelial cells of the distal tubule and collecting duct than in the proximal tubule. One previous study has reported GLCCI1 immunoreactivity in podocyte cytoplasm and the mesangial cells of mouse kidney [33], but more work is required to clarify the distribution of GLCCI1 expression in human kidney.

Several limitations of this study should be acknowledged. First, the study has a relatively small cohort size and was conducted in a single-center. Second, we could not assess the mRNA expression of *GLCCI1* because of the retrospective nature of the study. Third, although we collected native kidney-specimens from as many recipients as possible, only eight specimens were available for analysis. Moreover, the number of arterioles varied among these samples. Thus, selection bias cannot be excluded, although differences in arteriole GLCCI1 immunoreactivity between CC/CT and TT genotypes was statistically significant. Finally, we did not check the GLCCI1 genotypes of the donors used in this study.

Conclusion

We have found a significant association between the rs37972 polymorphism of *GLCCI1* promoter and post-transplant hypertension in renal transplant recipients.

Disclosure Statement

All authors have declared no competing interests.

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