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Klotho as a potential predictor of deceased donor kidney transplantation outcomes

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김 서 민

Abstract

Klotho as a potential predictor of deceased donor kidney transplantation outcomes

Suh Min Kim

Medicine

The Graduate School

Seoul National University

Background: Klotho is an anti-aging factor mainly produced by renal tubular cells. Klotho is reportedly decreased in an animal model of acute kidney injury and patients with chronic kidney disease. However, information on Klotho expression after kidney transplantation is limited. The correlation between donor Klotho expression and clinical outcomes of kidney transplantation was investigated.

Methods: Sixty patients who underwent deceased donor kidney transplantation between March 2015 and October 2017 were enrolled. Serum levels and tissue expression of Klotho were measured by enzyme-linked immunosorbent assay and immunohistochemistry, respectively. Graft function was assessed by estimated glomerular infiltration rate (eGFR).

Results: Recipients were divided into two groups according to donor Klotho expression in renal tissues. A greater improvement in eGFR was observed at 1 week after transplantation in recipients receiving kidneys with higher Klotho expression (47.5±21.9 vs. 63.9±28.2 ml/min/1.73m^2, P = 0.030). Recipients were dichotomized according to the median value of donor serum Klotho level. There was a tendency for a higher eGFR at 12 months after transplantation in recipients receiving kidneys from donors with a higher Klotho level (51.0±18.0 vs. 61.2±16.5 ml/min/1.73m^2, P = 0.059). When subgrouped into recipients with or without biopsy-proven acute rejection, 12-month eGFR remained higher in recipients receiving kidneys from donors with a higher serum Klotho level.

Conclusion: Donor tissue expression of Klotho was correlated with early recovery of eGFR after deceased donor kidney transplantation. Donor serum Klotho level tended to be associated with recipients post-transplant 12-month eGFR. Donor Klotho expression might be a new predictor for deceased donor kidney transplantation outcomes.

Keywords: Klotho, deceased donor, kidney transplantation

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Introduction

Klotho was first identified in 1997 as a novel aging suppressor gene (1). Mutation of the Klotho gene in mice was associated with several symptoms of premature aging, including arteriosclerosis, infertility, hypoglycemia, severe hyperphosphatemia, osteoporosis, and an overall shorter life span (1). The Klotho gene is located on chromosome 13 in humans. It encodes a single-pass transmembrane protein containing three members: α-Klotho, β-Klotho, and Klotho-related protein. α-Klotho is the dominantly present one (2). The kidneys have high protein levels of Klotho, and the majority is expressed in distal convoluted tubule cells (3). A small amount of Klotho was found in the choroid plexus epithelial cells in the brain, skeletal muscle, urinary bladder, aorta, ovary, colon, and thyroid gland (4, 5).

There are two forms of Klotho protein: a membrane form and a secreted form. The membrane form acts as a co-receptor for fibroblast growth factor-23 (FGF-23), and regulates phosphate absorption and $1,25(OH)_2D_3$ activity (2, 6). Recent studies suggest that Klotho also suppresses the insulin and Wnt signaling pathways (6). The extracellular domain of Klotho is cleaved on the cell surface by membrane-anchored proteases, and released into the blood, urine, and cerebrospinal fluid (6, 7). Secreted Klotho protein has multiple functions including regulation of multiple ion channels and oxidative stress (8). The function of secreted Klotho is less understood than that of the membrane form.

Klotho is downregulated in acute kidney injury in animal models (9, 10). Hu et al. showed that changes in Klotho level preceded the increase of creatinine or neutrophil gelatinase-associated lipocalin (NGAL) in mice with acute kidney injury (7). Sugiura et al. reported that renal fibrosis induced by unilateral ureter obstruction was severe in mice with reduced Klotho expression (11). Klotho mutant mice also showed defective endothelial function and impaired vasculogenesis (12). In addition, Klotho deficiency in mouse contributes to uremic cardiomyopathy, which can be prevented or attenuated by supplementation of soluble Klotho (13, 14).

In humans, Klotho deficiency was found in the early stage of chronic kidney disease (CKD) preceding disturbances in other parameters of mineral metabolism (15, 16). Seibert et al. showed that Klotho level was lower in CKD patients and correlated to eGFR (17). Sakan et al. showed reduced renal Klotho expression with progression of CKD (18). Krajisnik et al. reported that Klotho mRNA levels in parathyroid gland declined in parallel with decreasing eGFR (19). The correlation of Klotho and FGF23 or serum phosphorus level was also well investigated (15, 18, 20). Kitagawa et al. showed the association of serum Klotho with arterial stiffness in CKD patients (21). In addition, a recent study with 79 CKD patients showed that low serum Klotho was associated with cardiovascular mortality (22).

Some studies demonstrated changes in serum and urine Klotho levels in kidney transplant recipients and donors. In a study with 15 kidney transplant recipients and donors, urinary Klotho levels in recipients were significantly higher than baseline values (23). In another study with 10 kidney donors, the levels of soluble serum Klotho were significantly lower than the baseline levels after nephrectomy (24). However, research on the association of Klotho with kidney transplantation outcomes is lacking. This study was initiated to investigate the effect of donor Klotho on graft function in kidney transplantation.

The aims of this study were to measure serum level and renal tissue expression of Klotho in deceased donors and to identify the correlation between donor Klotho and clinical outcomes of kidney transplantation.

Materials and methods

Study population

Sixty patients who underwent deceased donor kidney transplantation between March 2015 and October 2017 and whose donor blood sample and/or renal tissues were available were enrolled in this study. This study was approved by the institutional review board of Seoul National University Hospital (IRB No.H-1611-048-807). The study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants. Blood samples for this study were provided by the Biobank of Seoul National University Hospital, a member of the Korea Biobank Network.

Donor blood samples and renal tissues

Blood samples of deceased donors were collected prior to organ recovery into a plain tube and stored at -80℃. An 18-gauge needle core biopsy of the cortex was taken at the time of implantation of the kidney in the recipient.

Klotho serum level

The Klotho level of donor serum was quantified by a solid phase sandwich enzyme-linked immunosorbent assay (ELISA) (Immuno-Biological Laboratories, Takasaki, Japan) according to the manufacturer`s instructions (23, 25).

Klotho immunohistochemistry

Klotho expression was identified by immunohistochemistry (26). Immunohistochemical staining was performed using the Discovery XT automated immunohistochemistry stainer (Ventana Medical Systems, Inc., Tucson, AZ, USA). Formalin-fixed, paraffin-embedded sections (4 mm thickness) were deparaffinized and antigen retrieval was performed using Tris-ethylenediaminetetraacetic acid (EDTA) buffer. Blocking of endogenous peroxides and protein was carried out using a 3% hydrogen peroxide (H_2O_2) solution. The kidney sections were incubated with 50µg/ml rat monoclonal anti-Klotho antibody (KM2076; TransGenic Inc. Japan) for 32 minutes at 37°C, and subsequently with secondary antibody for 20 minutes at 37°C. Slides were counterstained by hematoxylin and eosin reagent. Nonimmune normal IgG was used to replace primary antibodies as a negative control, and no staining occurred. Digital images were obtained using a Leica SCN400F device. The average percentage of staining tubule cells in five randomly selected fields was measured by a pathologist (27).

Immunosuppression

All of the patients received basiliximab as an induction therapy. Maintenance immunosuppression consisted of steroids, mycophenolate and calcineurin inhibitors.

Clinical outcomes

Graft function was assessed at 1 week and at 1, 3, 6, and 12 months after transplantation based on estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease (MDRD) equation**.** Delayed graft function (DGF) was defined as the need for hemodialysis within 1 postoperative week. Borderline change and rejection were determined according to the criteria proposed at the 2007 Banff Conference (28).

Histologic evaluation of kidney allograft

Protocol biopsy was performed 10 days and 1 year after transplantation. The number of non-sclerotic and globally sclerotic glomeruli was counted to determine the percentage of glomerulosclerosis(GS) (29, 30). The severity of interstitial fibrosis and tubular atrophy (IFTA) was graded according to the percentage of cortical area; 1, mild (<25% of cortical area); 2, moderate (25-50%);3, severe (>50%)(28).

Statistical analysis

Continuous data were summarized as the mean ± standard deviation and compared using a *t*-test and Mann-Whitney test. Categorical data were summarized as proportions and percentages and compared using the Chi-squared test or Fisher`s exact test. Regression analysis was used to evaluate the linear relationship between two continuous variables. Factors with $P < 0.20$ in univariate regression were entered into a multivariate analysis model. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 18.0 software (SPSS Inc, Chicago, IL).

Results

Serum Klotho level was not correlated with donor age

Blood samples obtained before organ recovery were available in 45 deceased donors. The mean serum level of Klotho was 629.3±354.6 pg/ml (median 528.9, range 157.6-1719.3 pg/ml). The serum Klotho level was not associated with either donor age (r=-0.074, $P = 0.622$) or donor final creatinine level (r=0.222, $P = 0.148$) (Figure 1).

Klotho expression gradually decreased in renal tissues

Renal tissue samples were obtained from 48 patients at the time of transplantation. The mean expression of Klotho in renal tissues was 86.6±10.6% (median 88.9, range 52.1-99.0%). The mean tissue expression of Klotho gradually decreased in serial kidney biopsies (86.6±10.6% at implantation, 77.9±14.5% at 10-day, and 72.3±14.1% at 1-year post-transplantation) (Figure 2).

Donor serum Klotho level was associated with post-transplant 12-month eGFR

The association of Klotho level and post-transplant eGFR was analyzed in two ways. Firstly, the recipients were divided into two groups according to the serum Klotho level of donors. Secondly, univariate and multivariate linear regression analysis were used**.**

There was no significant difference in the baseline characteristics between two groups divided by the donor serum Klotho level. The donors with a higher Klotho level were younger and showed lower incidence of hypertension and diabetes mellitus, although it did not reach statistical significance (Table 1). There was no significant difference in the incidence of DGF, biopsy- proven acute rejection (BPAR), and borderline changes in both groups (Table 2). The eGFR at 12 months after kidney transplantation tended to be higher in recipients receiving kidneys from donors with a higher serum level of Klotho (51.0±18.0 vs. 61.2±16.5 mL/min/1.73m^{2}, $P = 0.059$) (Figure 3).

Recipients were subgrouped into two groups with or without BPAR to exclude the influence of immunologic insult. Seven of 23 patients with a lower serum Klotho level and 6 of 22 patients with a higher serum Klotho level had at least one episode of BPAR. The eGFR at 12-month remained higher in recipients receiving kidneys from donors with a higher serum Klotho level (Table 3).

In regression analysis, there was no significant correlation between donor serum Klotho level and post-transplant eGFR at 12 months. In univariate analysis, kidney donor risk index (KDRI) donor age, and recipient body weight were correlated with post-transplant 12 months eGFR. Recipient body weight and final creatinine level of donors before organ procurement were confirmed as significant factors in multivariate analysis. Donor creatinine level showed a positive correlation with post-transplant 12-month eGFR in multivariate analysis (Table 4).

Klotho expression in donor renal tissue positively correlated with early recovery of renal function after kidney transplantation

When recipients were divided into two groups according to the expression of Klotho in the donor renal tissue, there was no significant difference in baseline characteristics. There was a tendency for a lower incidence of DGF in recipients receiving kidneys with higher Klotho expression, although it did not reach statistical significance (Table 2). Recipients with kidney grafts with higher Klotho expression showed a higher eGFR at 1 week after transplantation (47.5±21.9 vs. 63.9±28.2 mL/min/1.73m^2, P = 0.030). However, the differences were not maintained in the longer-term follow-up of eGFR (Figure 4).

In multivariate regression analysis, there was a significant association between donor renal tissue Klotho expression and recipients post-transplant 1-week eGFR (Table 5).

Klotho expression in donor renal tissue was related to GS in postoperative protocol biopsy

Kidney allografts with higher Klotho expression showed less degree of GS in protocol biopsies taken at 10 days and 1 year after transplantation compared to those with lower Klotho expression, although it did not reach statistical significance (Table 6). There were no significant differences in the degree of IFTA.

Discussion

Organ shortage and donor expansion are important issues in kidney transplantation. The proportion of grafts procured from expanded criteria donors has increased, which has led to an increased incidence of DGF and rejection (31). There is a need for biomarkers to predict the transplant outcomes and to evaluate organ suitability. Serum creatinine level is one of the common criteria for kidney transplantation. However, previous studies have shown favorable outcomes of transplantation from donors with high terminal creatinine (32, 33). Thus, it cannot be an absolute criterion. The decision to use a kidney with rising creatinine frequently depends on physician preference.

Histological findings are used to evaluate kidneys, although they are not included in the United Network for Organ Sharing criteria or KDRI. The degree of GS, IFTA, and hyaline arteriolosclerosis were reported to be associated with poor graft outcomes (34-36). Gaber et al. showed that GS greater than 20% increased DGF and resulted in poor transplant outcomes (37). However, there have been studies demonstrating limited values of procurement biopsy to determine whether or not to transplant a kidney (38, 39). In addition, because there are no defined criteria for which pathological findings can be used to evaluate organ suitability, the decision to discard a kidney varies across surgeons and centers.

Klotho is known to be deficient in the early stage of CKD. Both serum and urine Klotho levels were found to be associated with eGFR in patients with CKD (40). Moreover, Klotho has been previously suggested to be associated with CKD-mineral bone disorder (41). Contrary to the extensive research on Klotho in CKD, there is limited information on the changes of Klotho after kidney transplantation. Castellano et al. showed down-regulation of Klotho in 7 patients suffering from DGF (25). A recent article showed that serum Klotho level in donor was lower in older donors and it was negatively associated with short-term kidney transplantation outcomes (42).

In this study, donor renal tissue expression of Klotho was correlated to the recipient eGFR at 1 week after transplantation. Additionally, donor serum Klotho level tended to be associated with recipient eGFR at 1 year after kidney transplantation. Although these results are still preliminary in nature and only showed a tendency, they are meaningful in that it is one of the first attempts to verify a correlation between donor Klotho with renal function in kidney transplant recipients. In addition, this study was performed with donor samples which were obtained all over the county and deposited in a biobank. This study showed the role of biobank in transplantation research.

In the present study, the post-transplant 12-month eGFR in recipients receiving kidneys from donors with higher serum Klotho level tended to be increased. While the previous study only showed favorable outcomes at 1 month after transplantation, the recipients were followed up for a year in this study (42). Many factors can influence the post-transplant 12-month eGFR. There was no case with recurrence of primary disease or BK virus nephropathy, thus subgroup analysis according to the occurrence of BPAR was performed. The post-transplant 12-month eGFR remained higher in the higher donor serum Klotho level group. It means that the positive effect of serum Klotho level on 12-months eGFR remained when the influence of acute rejection was excluded. The association of serum Klotho and post-transplant eGFR was not confirmed in the regression analysis, thus further study with a larger cohort is warranted.

There was no correlation between serum Klotho level and donor age or donor final creatinine level, which are widely used parameters for organ suitability. It suggested that Klotho could be a new potential prognostic marker independent of donor age or serum creatinine level. There was no association between serum level and renal tissue expression of Klotho in donors. Firstly, this might be caused by the small number of patients included in this study. Secondly, the change of protein expression in tissues might be slower than alteration of blood Klotho level. Acute kidney injury could influence the serum level of Klotho especially in deceased donors. Serial measurement and analysis of the correlation between serum and tissue Klotho are required to show the concrete results.

Klotho is not only a biomarker, but also a potential therapeutic target for CKD and ischemic acute kidney injury (41). In animal studies, it has been demonstrated that administration of Klotho ameliorated kidney injury and renal fibrosis (7, 43-45). Reactivation of endogenous Klotho expression, delivery of Klotho cDNA, and administration of soluble Klotho protein are suggested methods of restoring Klotho levels (46). There were studies that investigated ways to modulate Klotho expression in kidney transplant patients, which included paricalcitol, erythropoietin and rapamycin (47-49). Application of Klotho during donor management as well as direct administration to recipients are possible ways to use Klotho in kidney transplantation.

There are limitations in this study. First, because it was an observational study with small number of patients, there was a limitation in the statistical analysis. The number of deceased donor is smaller in Korea compared to that of western countries. In addition, it is difficult to obtain informed consent from donor`s family all over the country. Although the result was promising, further validation with a large cohort is required. Second, both creatinine and Klotho levels can be influenced by acute kidney injury in deceased donors. Thus, detailed data on donors, such as length of stay in intensive care unit or episodes of hypotension, could be helpful to analyze the results. Lastly, the data on FGF-23 and vitamin D which were closely related to Klotho physiology could not be collected.

In conclusion, renal tissue expression of Klotho in donors was associated with immediate renal function after deceased donor kidney transplantation. Additionally, donor serum level of

Klotho tended to be correlated with recipients post-transplant 12-month eGFR. Donor Klotho expression could be a new predictor for deceased donor kidney transplantation outcomes. Further studies with larger number of patients are needed to validate the results.

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Tables

Table 1. Baseline characteristics according to donor serum Klotho level

	Serum level		
	Lower level	**Higher level**	***P***
	≤ 528.9 pg/ml	**>528.9 pg/ml**	
	n=23	**n=22**	
Age, mean±SD (years)	52.6±13.4	50.2±13.0	0.548
Female, n (%)	9 (39.1%)	6 (27.3%)	0.530
Hypertension, n (%)	13 (56.5%)	14 (63.6%)	0.763
Diabetes mellitus, n (%)	7 (30.4%)	8 (36.4%)	0.758
Duration of HD, mean±SD (months)	85.8±26.3	83.9±35.2	0.836
Graft weight, mean±SD (gram)	172.4±32.0	188.5±36.7	0.123
Cold ischemia time, mean±SD (minutes)	262.9±85.9	247.3±71.3	0.522
Warm ischemia time, mean±SD (minutes)	41.8±11.7	38.8±8.3	0.321
HLA mismatching, n	2.7±1.9	2.9±1.9	0.706
Donor age, mean±SD (years)	53.0±13.4	49.0±12.1	0.294
Donor hypertension, n (%)	11 (47.8%)	6 (27.3%)	0.356
Donor diabetes mellitus, n (%)	3 (13.0%)	1 (4.5%)	0.605
Cause of death, n (%)			0.675
Hypoxia	6 (26.1%)	6 (27.3%)	
Cerebrovascular accident	14 (60.9%)	12 (54.5%)	
Trauma	3 (13.0%)	2 (9.1%)	
Others	0	1 (4.5%)	
Final creatinine, mean±SD (mg/dL)	0.85±0.36	1.01±0.45	0.212
Kidney Donor Risk Index	1.3±0.5	1.2±0.3	0.421

HD: hemodialysis

Table 2. Kidney transplantation outcomes according to donor serum Klotho level and renal tissue Klotho expression

	Serum level		
	Lower level	**Higher level**	*P*
	≤ 528.9 pg/ml	**>528.9 pg/ml**	
	n= 23	**n= 22**	
Acute rejection			0.914
Borderline change	7 (30.4%)	8 (36.4%)	
Acute rejection	7 (30.4%)	6 (27.3%)	
Delayed graft function	2 (8.7%)	2 (9.1%)	0.999
eGFR (mL/min/1.73m^2)			
1 week	54.3±22.3	54.7±29.5	0.963
1 month	51.4±12.5	54.7±13.2	0.395
3 months	48.5±14.2	54.8±12.3	0.119
6 months	51.9±16.1	55.4±11.8	0.418
12 months	51.0±18.0	61.2±16.5	0.059
	Tissue expression		
	Lower expression	**Higher expression**	*P*
	≤ 88.9%	**> 88.9%**	
	n= 24	**n=24**	
Acute rejection			0.129
Borderline change	5 (20.8%)	9 (37.5%)	
Acute rejection	4 (16.7%)	7 (29.2%)	
Delayed graft function	4 (16.7%)	1 (4.2%)	0.348
eGFR (mL/min/1.73m^2)			
1 week	47.5±21.9	63.9±28.2	0.030
1 month	52.1±13.8	57.3±16.7	0.239
3 months	51.5±12.4	56.5±15.3	0.221
6 months	51.5±14.0	57.0±10.0	0.121
12 months	56.9±16.7	58.6±15.3	0.720

eGFR: estimated glomerular infiltration rate

Table 3. Post-transplant 12-month eGFR according to the serum level of Klotho in patients with and without BPAR

	Serum level		
	Lower level	**Higher level**	*P*
	≤ 528.9 pg/ml	**>528.9 pg/ml**	
BPAR	49.2±22.0	58.1±17.0	0.251
No BPAR	53.5±10.8	67.5±14.5	0.043
Total	51.0±18.0	61.2±16.5	0.059

eGFR: estimated glomerular infiltration rate, BPAR, Biopsy proven acute rejection

Table 4. Regression analysis on the donor- or transplant-related factors associated with post-transplant 12-month eGFR

	Univariate		Multivariate	
	β (95% CI)	***P***	**β (95% CI)**	***P***
KDRI	-15.813(-25.712,-5.914)	0.002	-3.512(-33.191,26.167)	0.811
Donor age	-0.465 (-0.763, -0.167)	0.003	-0.422 (-1.316, 0.472)	0.342
Final creatinine	8.153 (-0.080, 16.385)	0.052	12.356 (3.814, 20.899)	0.006
Degree of GS	-0.480 (-0.974, 0.013)	0.056	0.050 (-0.445, 0.546)	0.837
Recipient body weight	0.518 (0.075, 0.961)	0.023	0.565 (0.047,1.082)	0.034
CIT	-0.038 (-0.104, 0.028)	0.255		
WIT	0.092 (-0.359, 0.543)	0.685		
Serum Klotho level	8.358 (-9.3061, 25.776)	0.339		

β: unadjusted coefficients, R^2 for multivariate analysis = 0.38

KDRI: Kidney Donor Risk Index, GS: glomerulosclerosis, CIT: cold ischemia time, WIT: warm ischemia time

Table 5. Regression analysis on the donor- or transplant-related factors associated with post-transplant 1-week eGFR

	Univariate		Multivariate	
	β (95% CI)	***P***	**β (95% CI)**	***P***
KDRI	-7.645 (-22.769,7.479)	0.316		
Donor age	-0.258 (-0.747, 0.230)	0.294		
Final creatinine	-5.305 (-17.213, 6.603)	0.376		
Degree of GS	0.082 (-0.578, 0.742)	0.803		
CIT	-0.064 (-0.167,0.039)	0.217		
WIT	-0.542 (-1.221,0.137)	0.116	-0.306 (-1.007, 0.395)	0.384
Recipient body weight	-0.614 (-1.303,0.075)	0.080	-0.856 (-1.563,-0.149)	0.019
Tissue Klotho expression	1.060 (0.385,1.735)	0.003	0.892 (0.214, 1.571)	0.011

β: unadjusted coefficients, R^2 for multivariate analysis = 0.29

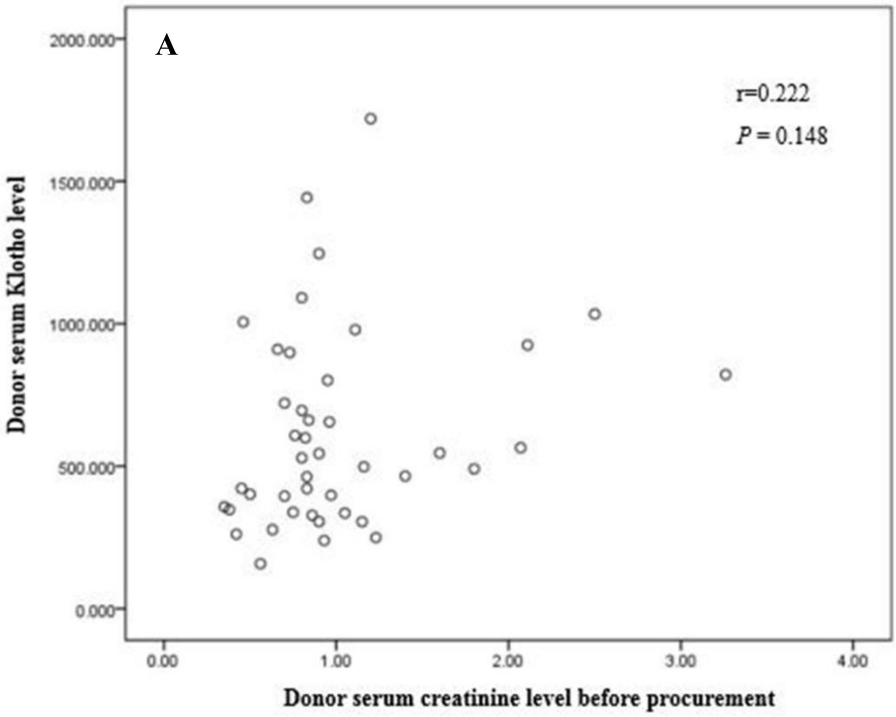
KDRI: Kidney Donor Risk Index, GS: glomerulosclerosis, CIT: cold ischemia time, WIT: warm ischemia time

Table 6. Pathological findings of protocol biopsy according to renal tissue Klotho expression

	Lower expression	**Higher expression**	*P*
	≤ 88.9%	**> 88.9%**	
	n= 24	**n= 24**	
Implant biopsy			
Glomerular sclerosis (%)	12.4±8.4	12.1±14.2	0.929
Interstitial Fibrosis	0.04±0.20	0	0.323
Tubular atrophy	0.04±0.20	0.04±0.21	0.976
10-day protocol biopsy			
Glomerular sclerosis (%)	11.2±7.8	6.7±5.6	0.087
Interstitial Fibrosis	0.13±0.34	0.04±0.20	0.292
Tubular atrophy	0.15±0.37	0	0.083
1-yr protocol biopsy			
Glomerular sclerosis (%)	15.0±8.9	8.9±8.3	0.226
Interstitial Fibrosis	0.50±0.71	0.46±0.78	0.904
Tubular atrophy	0.60±0.70	0.62±0.77	0.961

Figures

Figure 1. Correlation between serum Klotho level and (A) final creatinine level before procurement in donor and (B) donor age



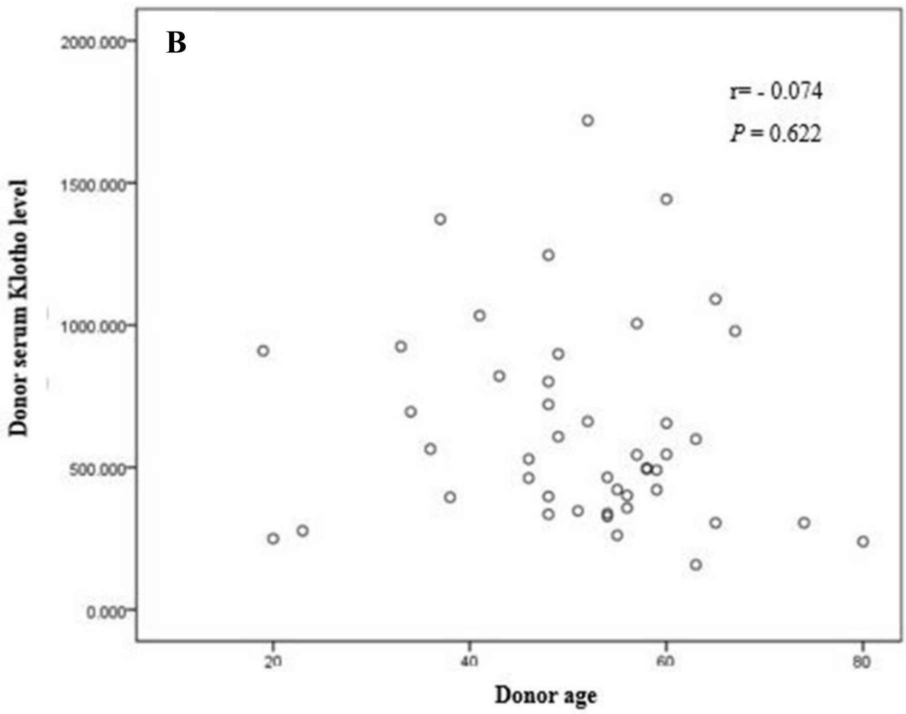
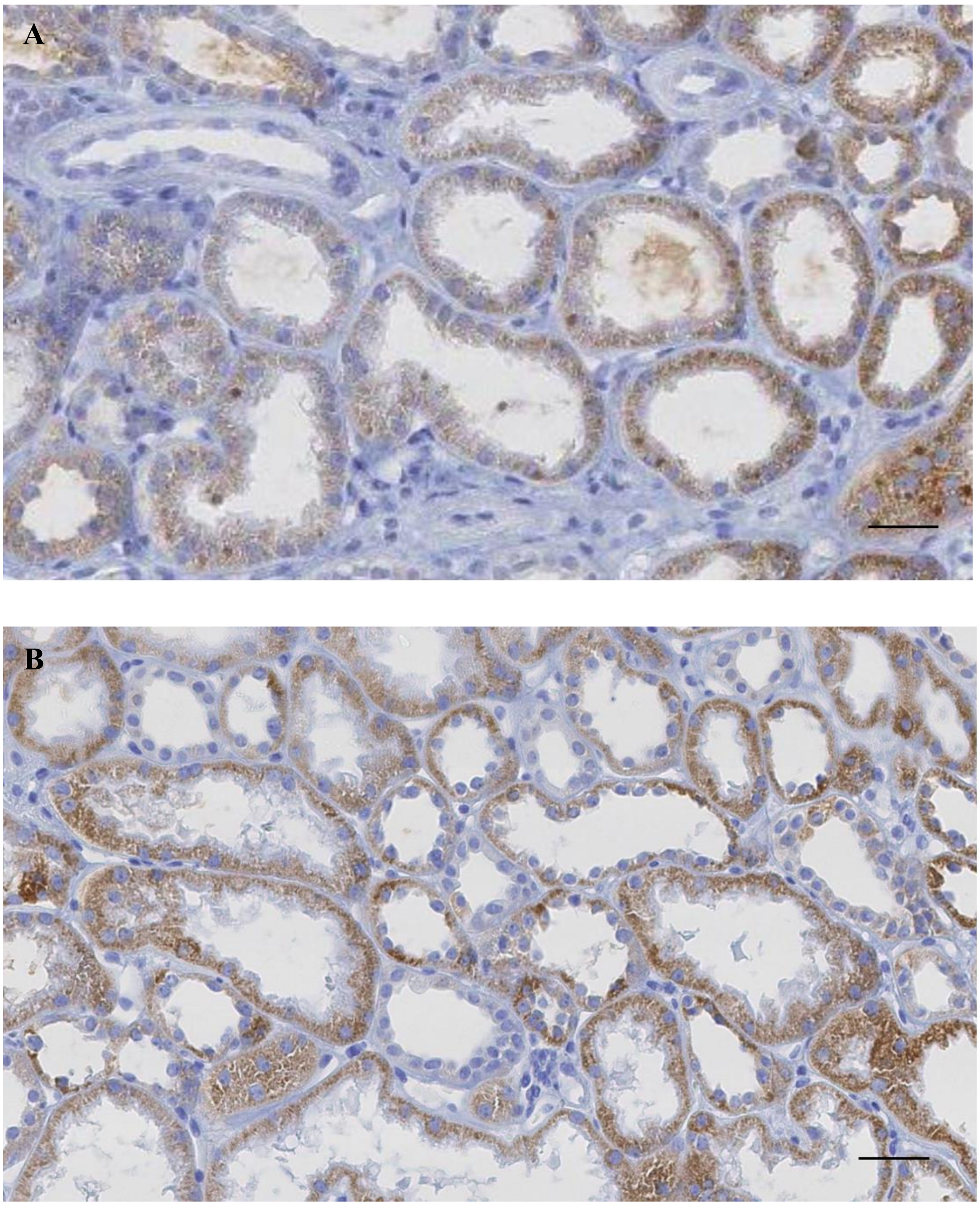
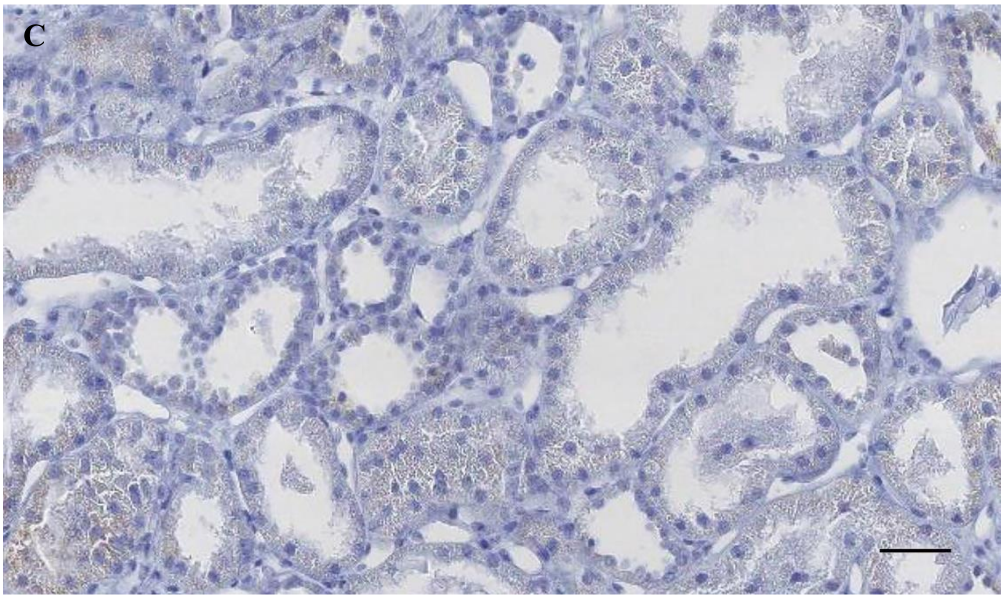

B
r= - 0.074
P = 0.622
Donor serum Klotho level
2000.000
1500.000
1000.000
500.000
0.000
20
40
60
80
Donor age

Figure 2. Representative immunohistochemistry images of (A) an implant, (B) a 10-day, and (C) an 1-year post-transplantation biopsy (magnification x 200, scale bar = 100µm). (D) Quantification of positive tubule cells in implant, 10-day, and 1-year post-transplantation biopsies.





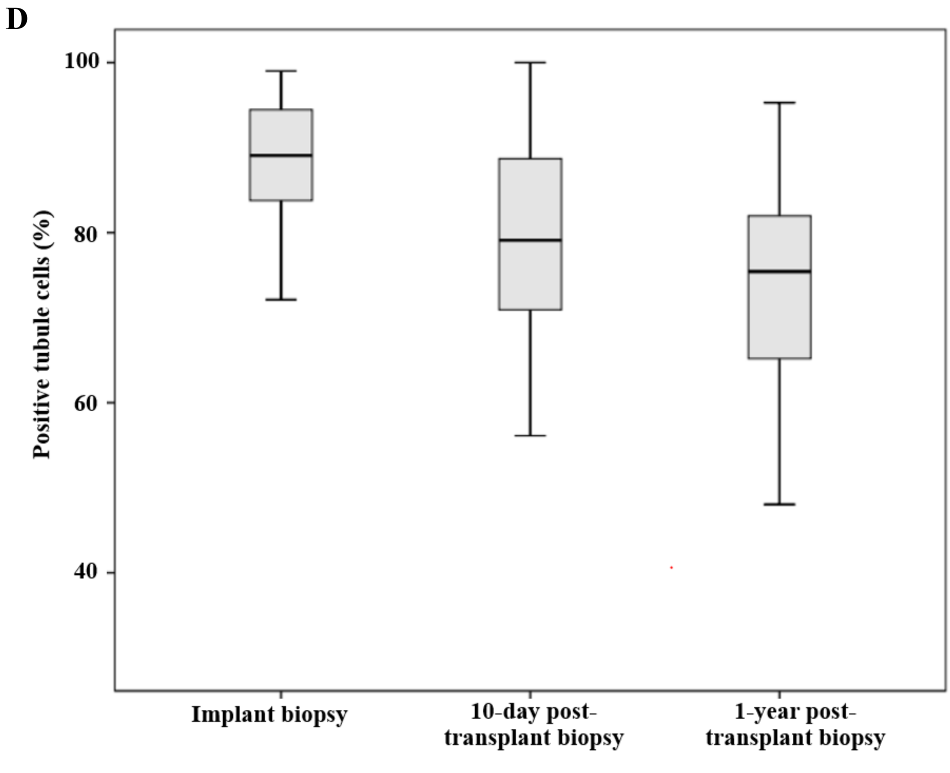

Positive tubule cells (%)
100
80
60
40
Implant biopsy
10-day post-transplant biopsy
1-year post-transplant biopsy

Figure 3. Post-transplant 12-month eGFR according to the serum Klotho level in donors

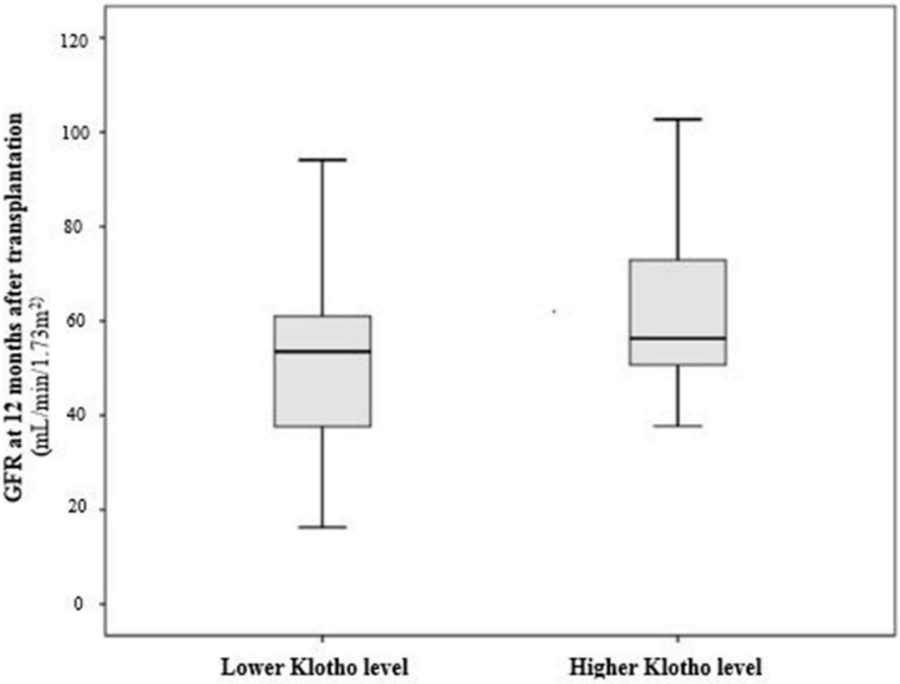
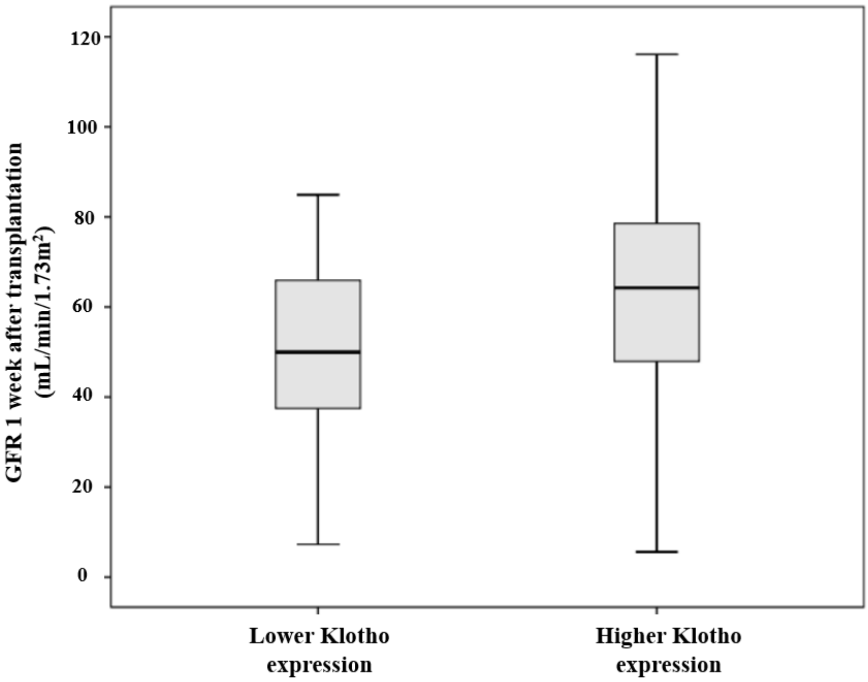


Figure 4. Post-transplant 1-week eGFR according to the renal tissue expression of Klotho in donors



국문초록

뇌사자 신장 이식의 결과 예측 인자로서 클로토의 의의

서울대학교 대학원

의학과 외과학 전공

김 서 민

배경: 클로토는 항노화 인자로 알려져 있으며, 신장의 원위세뇨관 세포에서 주로 발현된다. 여러 연구를 통해 클로토는 급성 신손상 동물 모델과 만성 신부전 환자에서 감소되는 것으로 알려져 있다. 클로토와 만성 신부전에 대한 많은 연구가 있으나, 신장 이식과의 연관성에 대한 연구는 많지 않다. 본 연구의 목적은 뇌사자 신장 이식에서 공여자의 혈액과 신장 조직에서 클로토 발현을 측정하여, 클로토 발현 정도와 신장 이식 결과의 연관성을 살펴보는 것이다.

방법: 본 연구는 2015년 3월부터 2017년 10월까지 뇌사 공여자 신장 이식을 받은 60명의 환자를 대상으로 하였다. 혈청의 클로토 농도는 효소면역측정법으로 측정하였고, 신장 조직의 클로토 발현은 면역조직화학염색법으로 측정하였다. 이

식편의 기능은 추정 사구체 여과율을 통하여 평가하였다.

결과: 대상 환자를 공여자의 신장 조직 클로토 발현 정도에 따라 두 군으로 나누어 분석하였다. 조직에서 클로토 발현이 높은 신장 이식편을 받은 환자가 이식 1주일 후 추정 사구체 여과율이 유의하게 높았다(47.5±21.9 vs. 63.9±28.2 ml/min/1.73m^2, P = 0.030). 대상 환자를 공여자의 혈청 클로토 농도에 따라 두 군으로 나누었을 때, 혈청 클로토 농도가 높은 공여자에게 신장 이식을 받은 환자가 이식 12개월 후 추정 사구체 여과율이 높은 경향을 보였다(51.0±18.0 vs. 61.2±16.5 ml/min/1.73m^2, P = 0.059). 대상 환자를 급성 거부 반응을 경험한 환자와 그렇지 않은 환자로 나누어 분석하였다. 급성 거부 반응 여부와 상관 없이 혈청 클로토 농도가 높은 공여자에게 신장 이식을 받은 환자가 이식 12개월 후 추정 사구체 여과율이 높았다.

결론: 본 연구를 통하여 뇌사자 신장 이식에서 공여자의 혈청 클로토 농도는 수혜자의 이식 12개월 후 추정 사구체 여과율과 관련되는 경향성을 확인하였다. 또한 공여자 신장 조직의 클로토 발현 정도는 이식 후 초기 신장 기능 회복과 유의한 관련성을 보였다. 뇌사자 신장 이식에서 공여자의 혈액과 신장 조직에서 클로토 발현은 이식편의 기능을 예측하는 인자로 고려해 볼 수 있다.

주요어: 클로토, 뇌사 공여자, 신장 이식

학번: 2012-31119