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〔Original Article〕

Impact of hypertension on long-term graft function after pediatric kidney transplantation: a 15-year follow-up of a Japanese regional cohort

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Abstract

Although hypertension is known to be strongly associated with short-term renal allograft dysfunction within 5 years after a pediatric kidney transplantation（KTx）, the long-term outcomes（＞10 years）are unclear. The present study retrospectively assessed the effect of hypertension on the estimated glomerular filtration rate（eGFR）decline in renal allografts over 15 years after KTx in pediatric recipients. Out of 49 pediatric KTx recipients, 31 with functioning grafts, i.e., an eGFR of more than 20 mL/min/1.73m^2 at 15 years after KTx, were included in the study. All the study participants completed the entire 15-year observation after their KTx. Recipients with any antihypertensive medications at 5 years after KTx were defined as hypertensive recipients, whereas those without antihypertensives were defined as normotensive recipients. The actual mean eGFR at 15 years after KTx was 24.3 mL/min/1.73m^2 in hypertensive recipients and 53.4 mL/min/1.73m^2 in normotensive recipients（P＜0.001）. The eGFR decline rate of the allograft among hypertensive recipients was distinct between the 10- and 15-year post-transplantation time points. In conclusion, our results demonstrated that hypertension had a significant negative impact on long-term pediatric renal allograft function and showed characteristic late deterioration 10 years after transplantation. Our findings suggest that hypertension may be a cause rather than a consequence of renal allograft dysfunction over time and emphasize the importance of longer post-transplantation follow-up（＞10 years）to clarify the influence of hypertension on graft function. Larger, prospective, long-term studies, including multidisciplinary early and sustainable blood pressure control trials, are warranted.

***Key words*: Pediatrics, kidney transplantation, hypertension, allograft dysfunction, long-term follow-up**

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Ⅰ. Introduction

Hypertension after kidney transplantation (KTx) in pediatric recipients is common, with a prevalence of 60-90%, 50-70%, and 40-60% at 3 months, 1 year, and 5 to 10 years post-KTx, respectively[1-6]. This trend has not changed for decades[7,8]. Ambulatory blood pressure monitoring (ABPM) and left ventricular hypertrophy (LVH) detected by echocardiogram have revealed that post-KTx hypertension in pediatric recipients continues to be underrecognized, underestimated, and suboptimally controlled[5,9-13]. Uncontrolled and persistent hypertension poses a pressing clinical issue: its effect on renal allograft outcomes together with cardiovascular complications later in the patients' life [14,15]. In short-term studies, hypertension within months or a year after KTx in pediatric recipients has been shown to be strongly and independently associated with allograft dysfunction up to 5 years post-KTx[1-3,7,16-18]. However, in longer observation periods of more than 5 to 10 years, the results are still inconclusive [4,5,11,12,19-23]. All previous long-term studies have used statistical predictions of the graft survival rates based on the data of various observation periods in individual study participants. However, the actual chronological changes in graft function, i.e., the annual estimated glomerular filtration rate (eGFR) decline pattern, in both recipients with and without hypertension have not been reported.

The present observational study aimed to examine the effect of pediatric post-KTx hypertension on long-term graft function and its chronological course, and retrospectively analyzed the renal allograft outcomes associated with pediatric post-KTx hypertension based on 15-year longitudinal follow-up of a Japanese regional cohort.

Ⅱ. Patients and methods

This study received ethics approval from Prefectural Okinawa Nanbu and Children's Medical Center's Institutional Review Board (ONCMC-IRB, No.29, January 19, 2017). Publication of the details of this study was also approved by the ONCMC-IRB. Informed consent was obtained from all the study participants after explaining the manner in which the study was to be conducted and the publication of the findings.

[Settings and participants] The present study was a retrospective, observational study conducted at two affiliated hospitals. Between August 1987 and November 2002, 49 pediatric patients requiring renal replacement therapy (RRT) by 16 years of age underwent their first KTx at Prefectural Okinawa Chubu Hospital (OCH), the regional center for pediatric KTx at that time. After the post-KTx follow-up at OCH, all 49 recipients were transferred to a newly developed pediatric end stage kidney disease (ESKD) program within Prefectural Okinawa Nanbu and Children's Medical Center (ONCMC) in April 2006. Continued pre- and post-KTx clinical care for all the recipients were organized by the same pediatric nephrologist who moved from OCH to ONCMC, together with other pediatric nephrologists at ONCMC and transplant surgeons at OCH. Of the 49 recipients, 5 died with functioning grafts, 8 resumed dialysis within 15 years after KTx (including 2 retransplant recipients, both of whom were excluded from this study). Five more recipients nearly required RRT due to an eGFR of 20 mL/min/1.73m^2 or less at 15 years post-KTx. The remaining 31 patients who had a functioning renal allograft (eGFR $>$20 mL/min/1.73m^2) at 15 years post-KTx were included in this study. The final observation point of the latest participant enrolled in this study was December 2017.

In this study, hypertension was defined as the use of antihypertensive medications. Recipients with regular antihypertensives at 5 years post-KTx were defined as hypertensive recipients (HRs) whereas those without any antihypertensives at 5 years post-KTx were defined as normotensive recipients (NRs). Each study participant was followed for 15 years after transplantation.

The patients' clinical data in their medical records relevant to post-KTx hypertension were age at KTx, sex, causes leading to ESKD, presence or absence of preemptive KTx, transplant era based

on immunosuppression protocol, donor source, immunosuppressant dosage at 5 years post-KTx, presence or absence of acute rejection episodes within 5 years post-KTx, presence or absence of antihypertensives at pre-KTx/1 year post-KTx/10 years post-KTx/15 years post-KTx, hypertension-associated comorbidities including metabolic vascular risk factors (overweight, hypertriglyceridemia, glucose intolerance) and experience of transition from pediatric to adult KTx care both at 10 years post-KTx, and the eGFR at 1 year post-KTx /5 years post-KTx/10 years post-KTx/15 years post-KTx. Cyclosporine A and tacrolimus were measured using a chemiluminescent enzyme immunoassay. Overweight, hypertriglyceridemia, and glucose intolerance were defined as more than 120% of the gender and height-adjusted median based on the Japanese pediatric data[24], more than 150 mg/dL, and more than 110 mg/dL of the fasting plasma glucose, respectively. The eGFR was calculated according to the formula for the Japanese pediatric population[25].

[Statistics] Categorical results were analyzed using the chi-square test and Fisher's exact test (for small sample sizes) when comparing variables between HRs and NRs. Numerical results were analyzed using Student's t test or the Mann-Whitney U test as appropriate and presented as the mean or median and standard deviation (SD) or interquartile range. $P < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using Microsoft Excel version 16051.11727.20230.0

Ⅲ. Results

Out of the 31 pediatric KTx recipients eligible for this study, at 5 years post-KTx, 17 (54.8%) were receiving one or more antihypertensives (HRs), and 14 (45.2%) were not receiving any antihypertensives (NRs). Initiation of antihypertensives was based on pediatric nephrologists' decisions at individual recipients' clinic visits by auscultatory blood pressure measurement using a mercury or an aneroid sphygmomanometer, resulting in adhering the most recent clinical practice guideline recommendations for all the study participants: stage 2 hypertension (≥95th percentile + 12mmHg or ≥140/90mmHg [whichever is lower] for children aged 1-13>, and ≥140/90mmHg for children aged ≥13) [26]. Table 1 summarizes the pre-KTx recipients' characteristics. HRs were significantly older at KTx, more often had non-CAKUT causes leading to ESKD, and more instances of dialysis before KTx. All preemptive transplants were performed for recipients with hypoplastic dysplastic kidneys, a major CAKUT causing ESKD. All the latter patients were NRs. Table 2 shows the transplant-specific conditions closely related to post-KTx hypertension. There was no significant difference between the HRs and NRs in terms of the transplant era, donor source, immunosuppressant administration at 5 years post-KTx or acute rejection episode within 5 years post-KTx. All living-related transplants gained immediate graft function, and 2 cadaveric transplants showed excellent recovery from

Table 1 Recipients' Demographics

Variables	Hypertensive n = 17	Normotensive n = 14	P value
Age at KTx*	10.4 (2.4-14.8)	3.3 (1.6-10.9)	<0.001**
Gender at KTx			
Male (18)	10	8	0.72
Female (13)	7	6	
Causes leading to ESKD			
CAKUT (15)	4	11	0.003**
Non-CAKUT (16)	13	3	
Preemptive KTx			
Yes (6)	0	6	0.021**
No (25)	17	8	

KTx: kidney transplantation, y: year, ESKD: end stage kidney disease, CAKUT: congenital anomaly of kidney and urinary tract

*Data are presented as median (interquartile range). **: statistical significance

Table 2 Transplant data associated with post-KTx HTN

Variables	Hypertensive	Normotensive	P value
Transplant era by immunosuppression			
1987-1993（CsA + AZA + mPSL）(5)	2	3	
1994-99（CsA + AZA + mPSL + ALG）(15)	9	6	0.55
2000-02（Tac + MMF + mPSL + Bx）(11)	6	5	
Donor Source			
LRD (29)	16	13	0.71
DD (2)	1	1	
Immunosuppression at 5-y post-KTx*			
CsA (ng/ml)	62.1 (31.2-73.6)	58.6 (33.4-81.2)	0.57
Tac (ng/ml)	2.8 (1.9-5.2)	3.1 (2.1-5.6)	0.48
mPSL (mg/kg)	0.12 (0.06-0.18)	0.11 (0.04-0.20)	0.52
Acute rejection episodes < 5-y post-KTx			
Yes (3)	2**	1**	0.58
No (28)	15	13	

HTN: hypertension, CsA: cyclosporine A, AZA: azathioprine, mPSL: methylprednisolone, ALG: antilymphocyte globulin, Tac: tacrolimus, Bx: basiliximab, LRD: live related donor, DD: deceased donor
*CsA/Tac/mPLS data are presented as median (interquartile range). **: acute rejection within 1-y post-KTx

Table 3 Long-term post-KTx HTN status

Variables	Hypertensive	Normotensive	P value
with Antihypertensives			
Pre-KTx			
Yes (13)	7	6	0.67
No (18)	10	8	
1-y post-KTx			
Yes (12)	11	1	0.001*
No (19)	6	13	
10-y post-KTx			
Yes (18)	17	1	<0.001*
No (13)	0	13	
15-y post-KTx			
Yes (19)	17	2	<0.001*
No (12)	0	12	

*: statistical significance

Table 4 Comorbidities associated with Post-KTx HTN

Variables	Hypertensive	Normotensive	P value
Overweight			
Yes (16)	13	3	0.012*
No (15)	4	11	
Hypertriglyceridemia			
Yes (13)	11	2	0.009*
No (18)	6	12	
Glucose intolerance			
Yes (7)	4	3	0.617
No (24)	13	11	
Experience of transition			
Yes (14)	11	3	0.029*
No (17)	6	11	

*: statistical significance

Table 5 Functional outcomes

Variables	Hypertensive	Normotensive	P value
eGFR (ml/min/1.73m²)			
1-year post-KTx	77.4 (7.9)	76.2 (7.8)	0.46
5-year post-KTx	68.6 (7.3)	69.9 (6.9)	0.31
10-year post-KTx	57.6 (6.9)	58.8 (5.4)	0.25
15-year post-KTx	24.3 (4.1)	53.4 (5.6)	＜0.001*

eGFR: estimated glomerular filtration rate
Data are normally distributed and presented as Mean (SD). *: statistical significance

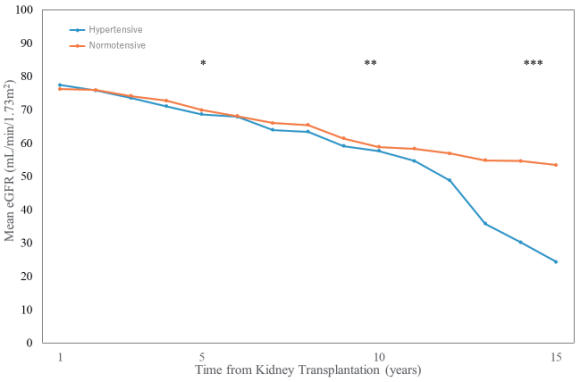

Fig. 1 Post-transplant graft function over time presented as the annual mean estimated glomerular filtration rate (eGFR)

*: P＝0.31, **: P＝0.25, ***: P＜0.001 as indicated in Table 5

an anuric period within a week. All 3 biopsy-proven acute rejection episodes occurred within a year and were reversed promptly with a few courses of bolus intravenous methylprednisolone administration. Table 3 shows the pre- and post-KTx hypertension status. Most HRs continued to require antihypertensives throughout the post-KTx period whereas most NRs did not. Table 4 shows the comorbidities, which may have caused and accelerated post-transplant hypertension, at 10 years post-KTx; these comorbidities, except for glucose intolerance, occurred significantly more often in HRs than in NRs. Table 5 shows the mean eGFR at 4 post-KTx time points; all the data in both groups were normally distributed with a narrow SD. The eGFR did not differ significantly between the HRs and NRs until 10 years post-KTx although the decline in the eGFR became significant among the HRs towards the 15-year post-KTx time point. The Figure shows changes in the mean annual eGFR corresponding to chronological changes in graft function, including a steep downward slope in the eGFR between 10 and 15 years post-KTx among the HRs in contrast to the stable eGFR among the NRs.

Ⅳ. Discussion

To the best of our knowledge, this is the first and the longest follow-up study to examine hypertension-associated allograft dysfunction in Japanese pediatric KTx recipients over 15 years. The following two characteristics of the present study may clarify the effect of hypertension on long-term graft function: the description of actual and contiguous eGFR changes in functioning grafts instead of statistical estimates of graft survival rates, and the observation of every study participant equally for a period of 15 years. The results showed two important clinical observations: post-KTx hypertension was significantly associated with allograft dysfunction, and graft function prominently deteriorated after 10 years post-KTx.

First, this study demonstrated that hypertension at 5 years post-KTx, already distinct at one year post-KTx and then persisted throughout the post-transplant course, was significantly associated with allograft renal dysfunction at 15 years post-KTx. It is conceivable that pediatric post-KTx hypertension is common within a year due to relatively high dosing of steroids/calcineurin inhibitors (CNIs) based on routine immunosuppressive protocols at the first year, and immunologic allograft conditions, e.g., acute rejection episodes/disease recurrence of primary kidney diseases resulting in higher maintenance dosing of immunosuppressants (steroids and CNIs)/consequent possible graft dysfunction, even in successful KTx gaining immediate graft function just after transplant surgery. However,

instead of resolving these episodes mostly within 12 months post-KTx, primary hypertension secondary to lifestyle issues in pediatric recipients with older age at KTx emerges at as early as 1 year post-KTx. In addition, secondary hypertension due to aforementioned immunologic events can be more prominent at 1 year after KTx and can persist afterwards, depending upon the severity of the events[14]. Previous studies showed mix results in long-term (>10 years) renal allograft outcomes associated with hypertension[4,5,11,12,20-23]. One possible explanation of this is the interstudy difference in the cohort demographics; reports showing no significant association between hypertension and graft outcomes focused on non-immunologic diseases causing ESKD (e.g., CAKUT), lower pre-KTx hypertension prevalence, and younger age at KTx [5,11,12,22]; in contrast, studies reporting opposite outcomes focused on non-CAKUT primary kidney diseases (e.g., focal segmental glomerulosclerosis [FSGS]), greater prevalence of pre-KTx hypertension, and older age at KTx[4,20,21,23]. In our study, although these parameter variables were comparably distributed in the cohort, HRs were significantly more numerous among older individuals and occurred more frequently with non-CAKUT diseases than in NRs (Table 1). Another possible reason is the difference in the definition of post-KTx hypertension, based on any of the following: (i) ABPM[5,11], (ii) office blood pressure measurement at patient visit[23], (iii) use of antihypertensive agents[4,21], (ii) + (iii)[24]or (i) + (ii) + (iii)[12,20]. Both short-term [16,17] and long-term studies have demonstrated clearly that defining post-KTx hypertension by the use of antihypertensives leads to a significant association between hypertension and poor graft survival[4,21]. One report emphasizing the superiority of defining post-KTx hypertension based on the use of antihypertensives showed an LVH co-occurrence rate of 37% in kidney transplant recipients with good control of hypertension due to the use of antihypertensives as measured by ABPM[12]. This may help to explain that good control of hypertension as measured by ABPM does not necessarily translate into favorable graft survival results; indeed, chronic hypertension (proven by LVH) before the normalization of blood pressure as measured by ABPM affects future graft outcomes. In our study, we defined hypertension based on the use of antihypertensives only, regardless of control status, whereas NRs were defined as those who were consistently non-hypertensive throughout their course, thus minimizing allocation bias[4,21]. Moreover, the distinct difference in eGFR decline over 15 years post-KTx between HRs and NRs suggests that hypertension *per se* may be considered to be a cause rather than a consequence of long-term renal allograft dysfunction.

Second, our continuing longitudinal observation revealed that the hypertension-associated decline in eGFR became more distinct after 10 years post-KTx than earlier. Previous, long-term studies statistically estimated the graft survival rate in recipients with hypertension at 15 to 20 years post-KTx to be approximately 40% of that at 5 to 10 years post-KTx[4,23]; however, unlike our study, these studies did not specify the allograft functioning status in the surviving grafts. The steeper eGFR decline seen in HRs between 10 and 15 years post-KTx may underscore the importance of longer periods of observation (>10 years) to evaluate how hypertension per se influences allograft outcomes. The accelerated eGFR deterioration after 10 years post-KTx could be the late effect of both metabolic vascular risk factors and transition-related non-adherence (NA) issues, precipitating hypertension. The metabolic vascular risk factors consisting of obesity, dyslipidemia and diabetes have been shown to be frequent in recipients with older age at KTx (around their pubertal periods), to coexist with, and to aggravate hypertension very often. This process as a whole, as metabolic syndrome, was significantly associated with allografts' significant but slow-and-steady eGFR decline in pediatric recipients via short- and medium-term observations within several years, although the impact of metabolic syndrome on long-term graft outcomes (>10 years) has yet to be determined[15,18,27,28]. Moreover, unstable, post-transition adherence to antihypertensives in adolescents and young adults (AYA) with KTx reportedly resulted

in suboptimal blood pressure control and poor long-term graft outcomes[6,9,13]. In the present study, these comorbidities at 10 years post-KTx were significantly more prevalent among HRs than among NRs (Table 4). Possible concrete explanations for this intense and long-lasting relationship between HRs and the comorbidities include that HRs predominantly consisted of (i) older-age-at-KTx recipients who could have become obese/hyperlipidemic/hypertensive after KTx due to early-developed and long-running undisciplined high caloric/salty eating habits by liberalized dietary restrictions/improved appetite without appropriate supervision and possible NA to antihypertensives, being established and consolidated by experience of transition, together with pubertal and post-pubertal psychosocial/emotional conflicts, (ii) more non-CAKUT primary diseases, represented by immunologic glomerular conditions with possible recurrence in renal allografts (e.g., FSGS), in that concomitant higher maintenance dosing of steroids/CNIs and graft dysfunction by the episodes could have evoked obesity/dyslipidemia/diabetes/hypertension, and (iii) no recipients with preemptive KTx, which has shown better long-term control of blood pressure, body weight, lipid metabolism, blood glucose, and health related quality of life by escaping uremia and dialysis [28], in that uremia and dialysis even only a little more than 1 year could have caused and sustained these comorbidities after KTx. Taken together, our results suggest that post-KTx hypertension, especially in the AYA age group, exacerbated by coexisting metabolic vascular risk factors and transition-related NA issues, may play an important role in late accelerated loss of graft function more than a decade after KTx.

Given these comorbidities, such as metabolic vascular risk factors and NA with transition in AYA age group, a number of studies have described the need for active, systems-based trials for improved blood pressure control among pediatric KTx recipients and have recommended strict ABPM, periodic LVH imaging by echocardiogram, better selection of antihypertensives, lifestyle modification programs, such as dietary counseling and daily exercise guidance, and structured transition programs from pediatric to adult post-KTx services[8,14,15]. However, to date, whether such meticulous long-term blood pressure control, starting immediately after pediatric KTx, leads to the preservation of long-term renal allograft function remains unclear.

This study has several limitations. First, the present observational study used a small sample size and analyzed the data retrospectively without randomization. Different immunosuppressants and antihypertensives were included without any analysis of possible differences in their individual effects. Second, only recipients with functioning grafts were included; therefore, the effect of hypertension on rapid graft loss was not investigated. However, excluding graft failure in this study may have shed light on how hypertension itself affects allograft renal function in the long run. Third, the definition of hypertension in this study was based on the use of antihypertensives only, rather than on actual measurements of blood pressure; however, given that the results of previous studies have demonstrated that graft function may not necessarily be preserved by the current status of well-controlled hypertension if there is a long history of uncontrolled hypertension, the definition of hypertension in the present study may not be inappropriate.

In conclusion, the present study showed that hypertension significantly influenced long-term renal allograft function over 15 years in Japanese pediatric KTx recipients. The eGFR decline rate accelerated after 10 years post-KTx. Our findings emphasize the importance of strict and prolonged post-KTx hypertension monitoring and control in pediatric recipients, especially among patients with older age at KTx, non-CAKUT primary diseases, metabolic syndrome related conditions, and transition to adult care. In the future, further studies with larger sample sizes should be conducted to elucidate how the aforementioned holistic approach to blood pressure control can improve long-term renal allograft outcomes in pediatric KTx recipients.

Contributors

HY conceived and designed the study. HY, TK, SF, MU, and KA were involved in data collection. HY, TK, SF, and MU analyzed and interpreted the data. HY, TK, SF, MU, KA, and NS were involved in the development, review, and approval of the manuscript. NS oversaw the whole process of writing the manuscript. Informed consent was obtained from all the study participants for the present study's preparation and publication, both of which were also approved by Institutional Review Board of Prefectural Okinawa Nanbu and Children's Medical Center（No. 29, January 19, 2017）.

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Conflict of interest

The authors declare that they have no conflicts of interest, either financial or non-financial, with regard to the content of this article.

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