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ORIGINAL ARTICLE

An Observational Cohort Study of the Effect of Hypertension on the Loss of Renal Function in Pediatric Kidney Recipients

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BACKGROUND
Post-transplant hypertension impacts negatively on renal graft survival. Our primary objective was to analyze the effect of hypertension on the glomerular filtration rate (GFR) slope.

METHODS
All clinical charts of children who underwent renal transplantation since the introduction of the routine use of ambulatory blood pressure monitoring (ABPM) were reviewed. Eligibility criteria for inclusion were measurement of GFR at 3 months, at 1 year post-transplant, and thereafter at yearly intervals; ABPM performed annually after transplantation; and functioning graft for a minimum of 2 years.

RESULTS
Sixty-eight (39 males) of 79 patients, aged 9.1 ± 5.3 years, met the inclusion criteria. The mean follow-up was 6.2 ± 2.8 years. Twenty-four patients had normotension or controlled hypertension throughout their follow-up (normotensive group). Forty-four patients had hypertension or noncontrolled hypertension at some point(s) during the follow-up period (hypertensive group). GFR slope was −1.6 ml/min/1.73 m^2 per year (95% confidence interval (CI = −3.7 to 0.4) in the normotensive group and −2 ml/min/1.73 m^2 per year (95% CI = −3 to −1.1) in the hypertensive group (P = 0.42). There was no difference between groups with regard to the change in GFR values from 3 months to 1 year and to last control (P = 0.87). At most recent control, the overall prevalence of controlled hypertension was 78.2% (95% CI = 63.6–89.1).

CONCLUSIONS
Although the results of our study are encouraging, they need to be confirmed in a larger prospective study using the same post-transplant follow-up protocol.

Keywords: ambulatory blood pressure monitoring; blood pressure; glomerular filtration rate; hypertension; left ventricular hypertrophy; pediatrics; transplantation.

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The majority of deaths in childhood kidney transplant recipients are from cardiovascular causes.[1] Pediatric renal transplant recipients with chronic allograft dysfunction are at high risk for the development of accelerated atherosclerosis and arteriosclerosis due to a combination of traditional and uremia-related risk factors.[2] Among the traditional risk factors, post-transplant hypertension is the most common predisposing determinant for cardiovascular disease.[3–5] Post-transplant hypertension often occurs in tandem with chronic kidney disease,[6] which not only remains the inevitable course of the transplanted kidney but is also an independent risk factor for cardiovascular disease.[7,8] As a consequence, correct diagnosis and reliable treatment response monitoring in hypertension are of eminent importance in the care of renal transplant recipients.[5,9] Pediatric studies have documented that the rate of renal function loss appears constant after successful renal transplantation.[10] However, changes in renal function in relation to blood pressure (BP) patterns over time has received less attention.[5]

At our center, renal function and BP are systematically measured by state-of-the-art methods at yearly intervals after transplantation. We reviewed computer-based hospital clinical charts of renal transplant recipients to assess the effect of hypertension on the loss of renal function. Our secondary objective was to determine the prevalence of left ventricular hypertrophy (LVH).

METHODS

Patients

This is a retrospective, single-center, consecutive case series study conducted in patients who were aged <18 years at the time they underwent kidney transplantation at our center between 1 January 1998, and 31 December 2010. Hospital ethics board approval was obtained for this study (protocol number 359.97). The last date of data collection was 31 December 2012. The specified time period allowed

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the systematic analysis of change in renal function and BP patterns over time. At our center, all renal transplant recipients undergo a protocolized annual control consisting of a more extended and comprehensive clinical laboratory examination, echocardiographic examination, and renal function test performed at yearly intervals.[11,12] Since 1998, ambulatory BP monitoring (ABPM) has been introduced as a routine post-transplant procedure at all annual controls.[12]

Eligibility criteria for inclusion were completeness of the data on renal function tests and ABPM throughout the follow-up period and functioning allograft for a minimum of 2 years.

The examined patients' characteristics included sex, cause of original renal disease, pretransplantation therapy modality, source of transplanted kidney, age at transplantation, weight, height, body mass index, acute rejection episodes, current medication (i.e., immunosuppressant and antihypertensive therapy at most recent annual control), and date of transfer from pediatric to the adult transplant unit.

From a total of 79 patients who were considered to be potentially eligible, 6 patients were excluded because of unavailable ABPM data, and 5 patients were excluded because of lack of renal function tests. The cohort study was comprised of a total of 68 patients (39 males, 29 females) who were transplanted at the mean (± SD) age of 9.1 ± 5.3 years (range = 0.8–16.8). The mean follow-up time from the date of transplant surgery was 6.2 ± 2.8 years (range = 2–13), and mean patients' age at most recent annual control was 15.3 ± 4.5 years (range = 4.2–20.8). Preemptive transplantation was performed in 32 of 68 patients. Fifty-seven patients received a kidney from living donors, and 11 received a kidney from deceased donors. Sixty-two patients underwent their first transplantation, 4 underwent their second, and 2 underwent their third. All patients had functioning allograft during the follow-up period.

The etiology of primary renal disease was hereditary in 22 patients, obstructive uropathy and renal hypo/dysplasia in 27, glomerulopathies in 11, neonatal acute kidney injury in 3, metabolic disease in 2, and unknown etiology in 3.

Assessment of graft function

Glomerular filtration rate (GFR) was determined at 3 months and at 1 year from the date of transplantation and thereafter at yearly intervals (i.e., at every annual control). Renal function was measured by the renal clearance of inulin (Inutest, 25%; Laevosan Gesellschaft, Linz, Austria) during water diuresis with a standard clearance technique including continuous infusion.[13] Since 2008, renal function has been measured by determining the plasma clearance of iohexol after a single injection, as previously described.[12] Overall, 478 tests were performed throughout the follow-up period. The individual annualized change in GFR was calculated using simple linear regression and based on GFR from 3 months post-transplant. The GFR slope is expressed as milliliters per minute per 1.73 m^2 per year. A negative GFR slope denotes a decline in GFR. Chronic kidney disease was defined as a sustained GFR <60 ml/min/1.73 m^2.[14]

Assessment of ambulatory blood pressure

ABPM was conducted with the oscillometric monitor model 90207 (Space Labs, Redmond, WA), which has been validated independently for precision and reliability in children and adolescents.[15] BPs were recorded on the nondominant arm using an appropriate arm cuff and were obtained every 20 minutes from 7 AM to 10 PM and every 30 minutes from 10 PM to 7 AM, as previously described.[12] Components of the ABPM retrieved for analysis included the 24-hour, daytime, and nighttime mean systolic and diastolic BPs, as well as mean arterial pressure values. Patients ABPM values were compared with published pediatric normative data for ABPM.[15] Patients ambulatory BP statuses were defined as follows: (i) normotension: mean daytime and nighttime systolic and diastolic BP values ≤95th distribution-adjusted height- and sex-related percentile for daytime and nighttime described in the published pediatric normative data for ABPM; (ii) controlled BP: mean daytime and nighttime systolic and diastolic BP readings within the normotensive range while the patient was on antihypertensive therapy; (iii) hypertension: mean daytime and/or nighttime systolic and/or diastolic BP value(s) >95th distribution-adjusted height- and sex-related percentile for daytime and nighttime; and (iv) noncontrolled hypertension: mean daytime and/or nighttime systolic and/or diastolic ambulatory BP reading(s) within the hypertensive range while the patient was on antihypertensive therapy.[15] In patients aged >18 years old, BP statuses were defined based on the recommendations provided by the European Guidelines for the management of hypertension.[16] Consequently, normotension and controlled hypertension (i.e., ambulatory BP values within the normotensive range while the patient was on antihypertensive therapy) were defined as average 24-hour systolic and diastolic BP values ≤130/80 mm Hg. Hypertension and noncontrolled hypertension (i.e., ambulatory BP values within the hypertensive range while the patient was on antihypertensive therapy) were defined as average 24-hour systolic and diastolic BP values >130/80 mm Hg.

Overall, 410 ABPMs were performed throughout the follow-up period.

Echocardiographic assessment of left ventricular mass

Left ventricular mass (LVM) derived from echocardiographic measurement obtained at the most recent annual control was calculated as proposed by Devereux *et al.*[17] and indexed to height in meters to the power of 2.7.[18] LVH was defined as LVM values >95th age- and sex-specified pediatric normative reference intervals.[19] In recipients aged >18 years, LVH was defined as LVM index >51 g/$m^{2.7}$.[20] All measurements were performed by the same investigator (G.V.), who was unaware of the patients' BP status. Because of technical problems, echocardiography data were not available for 3 patients. Intraobserver reliability was calculated from 10 paired measurements. The coefficient of variation for measurements of LVM was 3.8%.

Statistical analysis

Statistical analysis was performed using Statistica version 10.0 (StatSoft for Windows, Tulsa, OK).

Because the cohort study underwent ABPM at yearly intervals after transplantation, we accept the premise that ABPM results obtained at each annual control reflected the patient's previous year's BP pattern. Consequently, we computed patient's post-transplant cumulative incidence of hypertension by summing the number of yearly periods of hypertension and noncontrolled hypertension. The cumulative incidence of post-transplant hypertension (i.e., the time the patient was exposed to hypertension) is expressed as the percentage of the entire follow-up period and as the corresponding time in years. The same approach was applied to estimate the post-transplant cumulative incidence of the composite of overweight and obesity status. Overweight and obesity status was defined by using international diagnosis criteria.[21]

Normal distribution of data was examined by means of measurement of skewness and kurtosis. Differences in group characteristics were assessed by χ^2 test for categorical variable and by independent *t* test for continuous variables. Comparison of data derived from 3 months post-transplant, 1 year post-transplant, and from the most recent annual control were analyzed using one-way analysis of variance repeated-measures design followed by a *post hoc* Scheffé test to allow multiple pairwise comparisons. Analysis of covariance was used to detect changes in GFR slope between normotensive and hypertensive patients with data derived both from 3 months post-transplant and from the entire follow-up period as covariables.

The GFR slope is expressed as the mean with 95% confidence intervals (CIs). All other values are expressed as mean and SD, unless otherwise indicated. A 2-tailed level of $\alpha < 0.05$ was considered significant in all analyses.

RESULTS

There was a significant decrease in the GFR of the cohort study during the follow-up period, from 69.9 ± 23.2 ml/min/1.73 m^2 at 3 months post-transplant to 57.6 ± 19.3 ml/min/1.73 m^2 at the most recent annual control ($P < 0.01$). The GFR declined at the mean rate of −1.9 ml/min/1.73 m^2 per year (95% CI = −2.8 to −0.9) from 3 months post-transplant.

Forty-four patients were identified as having been diagnosed with hypertension or noncontrolled hypertension at some point(s) in the course of their follow-up (hypertensive group), whereas 24 patients were regarded as having been normotensive or had controlled hypertension throughout the entire post-transplant follow-up time (normotensive group). In the hypertensive group, the mean cumulative incidence of post-transplant hypertension over time was 2.5 years (95% CI = 1.9–3.2), which represented 39% (95% CI = 31%–47%) of their follow-up period. There was no significant difference between the hypertensive and normotensive group in their effect on the GFR slope ($P = 0.53$). Additionally, we did not observe a significant difference between preemptive vs. nonpreemptive transplantation in their effect on the GFR slope ($P = 0.58$). Similarly, no significant correlation was observed between the cumulative time incidence of the composite of overweight and obesity status and post-transplant BP patterns on the GFR slope ($P = 0.66$).

Further analysis of the data of normotensive and hypertensive patients showed that there were no group differences for age at transplantation, sex, source of transplanted kidney, pretransplant therapy modality, duration of follow-up, weight, height, body mass index, and the cumulative incidence of the composite of overweight and obesity status (Table 1). Overall, at most recent annual control, 35 patients were on a triple-drug immunosuppressive regimen consisting of tacrolimus, azathioprine, and prednisolone; 15 patients were on tacrolimus, mycophenolate mofetil, and prednisolone; 1 patient was on cyclosporine A, azathioprine, and prednisolone; and 17 patients were on an immunosuppressive protocol based on tacrolimus and prednisolone.

Fifteen patients in the normotensive group and 24 patients in the hypertensive group had chronic kidney disease at the most recent annual control ($P = 0.52$). The mean decline in GFR from 3 months post-transplant was −1.6 ml/min/1.73 m^2 per year (95% CI = −3.7 to 0.4) in the normotensive group compared with −2 ml/min/1.73 m^2 per year (95% CI = −3 to −1.1) for the hypertensive group ($P = 0.42$) (Table 2). There was no difference between the normotensive and the hypertensive group with regard to the change in mean GFR values from 3 months to 1 year post-transplant and to the most recent annual control ($P = 0.87$) (Table 3). However, there was a statistically significant decrease in mean GFR levels in both groups over time ($P < 0.001$).

Ambulatory BP results and BP status and antihypertensive therapy in the normotensive and the hypertensive group at their most recent annual control are shown in Table 4. Twenty-four-hour and nighttime systolic BP values and nighttime mean arterial pressure values were significantly lower among patients in the normotensive group than in the hypertensive group (Table 4). At most recent control, the overall prevalence of good BP control was 78.2% (95% CI = 63.6%–89.1%).

Three patients in the hypertensive group (Table 4) and 2 patients in the normotensive group (data not shown) were successfully withdrawn from antihypertensive medication.

At the most recent annual control, mean LVMI values in the normotensive and hypertensive group were 28.28 ± 9.74 18 g/$m^{2.7}$ and 29.65 ± 7.18 g/$m^{2.7}$, respectively ($P = 0.52$). At that time, 1 of 23 patient in the normotensive group and 4 of 42 patients in the hypertensive group had LVH ($P = 0.45$). Overall, the prevalence of LVH at the most recent annual control was 7.6% (95% CI = 2.5%–17.0%).

DISCUSSION

The primary objective of this study was to address whether hypertension precipitates the loss of GFR after transplantation. We found that post-transplant hypertension, defined as the summation of time periods of 1 year with either newly diagnosed hypertension or noncontrolled hypertension, did not accelerate the rate of loss of GFR compared with patients

Table 1. Characteristics of the normotensive and hypertensive group

Variables	Normotensive (n = 24)	Hypertensive (n = 44)	*P* value
Age at Tx, y	8.8 ± 5.6	9.2 ± 5.2	0.71
Sex, M/F	13/11	26/18	0.69
Donor, L/D	19/5	38/6	0.44
Preemptive Tx	10	22	0.51
Acute rejection episodes	4	5	0.53
Follow-up, y	5.4 ± 2.6	6.5 ± 2.9	0.10
Weight, kg			
3 months post-Tx	35.5 ± 21.1	37.6 ± 20.3	0.68
1 y post-Tx	38 ± 20.9	41.9 ± 21.9	0.45
Last follow-up[a]	54.1 ± 22.9	59.8 ± 19.9	0.28
Height, cm			
3 months post-Tx	124.6 ± 31.8	129.1 ± 31.8	0.58
1 y post-Tx	128.9 ± 29.6	132.3 ± 34.1	0.68
Last follow-up[a]	149.7 ± 21.3	156.9 ± 17.7	0.14
BMI, kg/m^2			
3 months post-Tx	20.4 ± 4.7	20.6 ± 4.2	0.68
1 y post-Tx	20.7 ± 4.7	21.3 ± 4.6	0.61
Last follow-up[a]	22.9 ± 5.6	23.7 ± 5.6	0.59
Overweight/obesity, y[b]	2.2 ± 2.8 (41.9 ± 45.6)	3 ± 3.2(43.8 ± 42.1)	0.29 (0.86)

Data are presented as mean ± SD unless otherwise indicated. Pre-emptive transplantation denotes kidney transplant procedure performed before dialysis.

Abbreviations: BMI, body mass index; D, dead; L, living; Tx, transplantation.

[a]Last follow-up indicates most recent annual control.

[b]Overweight/obesity indicates post-transplant cumulative incidence over time expressed in years; as percentage is given in parentheses.

Table 2. Glomerular filtration rate in the normotensive and hypertensive group over time

Variables	Normotensive (n = 24)	Hypertensive (n = 44)
GFR, ml/min/1.73m^2		
3 months post-Tx	70.6 ± 26.7	69.7 ± 21.5
1 y post-Tx	69.2 ± 21.6	67.8 ± 21.4
Last follow-up	56.7 ± 21.1	58.2 ± 18.6

Data are presented as mean ± SD.

Abbreviations: GFR, glomerular filtration rate; Tx, transplantation.

Table 3. Results from analysis of covariance for analysis of glomerular filtration rate at 3 months, 1 year, and at most recent annual control (last follow-up), including group of patients as a fixed factor

Group Time	Mean	SE	95% CI	No.
NT 3 months	70.6	4.8	61.0–80.1	24
NT 1 y	69.2	4.4	60.4–77.9	24
NT Last F-U	56.7	4.0	48.7–64.6	24
HT 3 months	69.7	3.5	62.6–76.7	44
HT 1 y	67.8	3.2	61.3–74.2	44
HT Last F-U	58.2	2.9	52.3–64.0	44

Data are presented as mean (least square mean), standard error (SE), and 95% confidence interval (CI).

Abbreviations: F-U, follow-up; HT, hypertensive group; NT, normotensive group.

who had normotension or controlled hypertension throughout the follow-up period.

Data derived from the largest pediatric renal transplant registry indicate that hypertension has a negative association with long-term estimated GFR.[10] Importantly, in that report, the use of antihypertensive medication was used as a surrogate of measured BP, and therefore no information can be provided on the quality of BP control. On the other hand, results from a small pediatric prospective investigation showed that ambulatory hypertension during a 2-year period had a negative impact on the estimated GFR.[22] A previous retrospective study based on office BP readings also found that post-transplant hypertension was significantly associated with overall worse kidney allograft survival.[23] Of note, we have previously demonstrated that the routine use of ABPM after transplantation provides a more clinically

Table 4. Ambulatory blood pressure results, blood pressure status, and antihypertensive therapy in the normotensive and hypertensive groups at their most recent annual control

Variables	Normotensive (n = 24)	Hypertensive (n = 44)	*P* values
SBP, mmHg			
24-h	109.6 ± 10.2	116.6 ± 13.3	0.02
Daytime	113.9 ± 9.4	118.6 ± 11.7	0.09
Nighttime	104.1 ± 11.6	111.6 ± 12.9	0.02
DBP, mmHg			
24-h	66.4 ± 7.1	69.5 ± 9.6	0.16
Daytime	70.6 ± 5.8	72.7 ± 9.8	0.33
Nighttime	60.1 ± 9.1	64.2 ± 7.9	0.08
MAP			
24-h	81.9 ± 7.2	86 ± 9.8	0.07
Daytime	85.5 ± 6.1	88.8 ± 10.1	0.15
Nighttime	76.1 ± 8.8	81.1 ± 9.6	0.04
BP status, No.			
Normotensive	16	3	—
Controlled HT	8	28	—
Noncontrolled HT	—	10	—
New onset HT	—	3	—
Antihypertensive			
ACEI	2	18	—
ARB	2	2	—
CCB	—	1	—
β-B	1	5	—
Diuretics	—	1	—
ACEI + CCB	—	3	—
ACEI + CCB + β-B	—	3	—
ACEI + CCB + diuretics	—	2	—
ACEI + β-B	1	1	—
ARB + CCB	—	1	—
ARB + β-B	2	2	—
ARB + diuretics	—	1	—
ARB + CCB + β-B	—	1	—

Data are presented as mean ± SD unless otherwise indicated.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; β-B, beta blockers; BP, blood pressure; CCB, calcium-channel blockers; DBP, diastolic blood pressure; HT, hypertension; MAP, mean arterial pressure; SBP, systolic blood pressure.

relevant readout compared with office BP readings on the quality of BP control.[24,25] Also, given the superiority of ambulatory over office BP measurements, not only in predicting fatal and nonfatal cardiovascular events[26] but also in predicting treatment-induced regression of LVH,[27] our results may provide a better estimate on the magnitude of change in renal function that would be expected in patients with hypertension. Our data may also indicate that longer periods of exposition to hypertension than those observed in our cohort study may be necessary for a negative effect on GFR. In accordance with our inference, a large collaborative retrospective study showed that adult renal transplant recipients with poor BP control, defined as office systolic BP values measured at 1 and at 3 years post-transplant ≥140 mm Hg would significantly benefit in terms of functioning graft at 10 years post-transplant if their systolic BP at 5 years post-transplant was controlled to <140 mm Hg.[28]

Equally important, most of our renal function data rely on a gold-standard technique for the measurement of GFR (i.e., renal clearance of inulin). In the aforementioned pediatric studies, creatinine-based estimation equation was the method of assessing post-transplant renal function.[10,22,23] In a recently published study from our group, we demonstrated that plasma clearance of iohexol correlates with renal

clearance of inulin and that plasma clearance of iohexol is significantly superior in predicting actual GFR than a creatinine-based estimation equation.[29] Although the latter is very valuable for providing estimates of renal function,[30] accurate methods for measuring glomerular filtration rate, as used in our study, would be most desirable when allograft function is used as a primary endpoint.

LVH is a reversible factor linked to cardiac death that is dependent on BP.[31] The low prevalence of LVH observed in our study might further underlay the benefit from applying ABPM systematically for evaluation and management of post-transplant hypertension.

Post-transplant obesity compromises the long-term graft and patient survival.[32] In our center, all transplant recipients are annually assessed by a nephrology-specific registered dietician and receive individually tailored dietary advice, including nonpharmacologic measures in hypertensive patients.[12] The high prevalence of increasing body mass index observed in our study calls into question our current approach to prevent post-transplant overweight and obesity status, pointing out that additional clinical strategies should be contemplated.

Although the outcomes of our study cohort (i.e., the annualized change in GFR and the low prevalence of hypertension and LVH over time) are encouraging, they must be interpreted in the context of the study design.[33] The major weakness of our retrospective cohort study is that no causal inference on the effect of intervention on the rate of loss in post-transplant renal function and regression of LVH can be made.[33] Another weakness is that patients were not randomly assigned to the exposure variable of interest (i.e., hypertension). However, based on the irrefutable evidence that controlled hypertension provides health benefits,[34] such a study is ethically impracticable.[35]

Finally, it is well established that kidney transplantation is the treatment of choice for end-stage renal disease because it prolongs[36] and improves quality of life.[37,38] Because the major cause of post-transplant morbidity and mortality is not renal but cardiovascular,[1] controlled hypertension is a desirable endpoint. Our current and previous data strongly support that the routine use of ABPM is a very valuable clinical tool for early diagnosis and treatment monitoring of post-transplant hypertension.[12,24,25,39] It seems that years of hypertension can be successfully treated without having a negative effect on renal function and on LVM. However, this remains to be confirmed in a larger prospective study that will also allow the comprehensive analysis of other variables of interest on the loss of renal function, such as the rate of graft rejection and high body mass index. It should be stressed that our cohort study included almost all patients who were consecutively transplanted from the systematic introduction of ABPM. In addition, the data were 100% complete for GFR and ABPM throughout the entire follow-up, and echocardiographic assessment was available in almost all of the recipients at their most recent annual control. Consequently, our results may be more generalizable to clinical practice[35] and be used by health providers as a framework for the diagnosis and follow-up of post-transplant hypertension.

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R.T.K. had the original idea and wrote the manuscript. C.C., U.B.B., and G.T. provided the data. G.V. did the analysis of echocardiography. U.B.B. has domain knowledge in GFR measurements. R.T.K. and J.K. did the statistical analysis. All the authors discussed the interpretation of the results and critically reviewed the final version of the manuscript. R.T.K. will act as the guarantor for the paper.

DISCLOSURES

The authors declared no conflict of interest.

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