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ORIGINAL ARTICLE

Post-transplant hypertension in pediatric kidney transplant recipients

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Abstract
Background The aim of the study was to investigate the prevalence of post-transplant hypertension (HT) and to assess the blood pressure (BP) of transplanted children with possible risk factors.
Methods Office and ambulatory blood pressure measurements were performed for each patient.
Results Twenty-nine patients were included in the study, including 13 patients with newly diagnosed untreated HT according to the results of ambulatory blood pressure monitoring (ABPM). Fourteen patients were on antihypertensive medication, but only in five of these patients was the HT under control; nine patients receiving antihypertensive drugs had uncontrolled HT. Of the 29 patients, two had normotension without any antihypertensive drug(s). Standard deviation scores (SDS) of the nocturnal diastolic BP of the ABPM were positively correlated with the prednisolone dosage per kilogram (p=0.013, r=0.45) and negatively correlated with the time period after transplantation (p=0.024, r= −0.41). Similarly, the SDS of the 24-h diastolic BP was positively correlated with the prednisolone dosage per kilogram (p=0.006, r=0.50) and negatively correlated with the time period after transplantation (p=0.016, r= −0.44). Patients with alternate-day steroid treatment had lower nocturnal systolic (p=0.016), nocturnal diastolic (p=0.001) and 24-h diastolic (p=0.008) SDS when compared to those receiving daily steroid medication.
Conclusion The prevalence of HT among children after renal transplantation was high among our patient cohort, and steroids had direct impact on nocturnal and diastolic BP.

Keywords Renal transplant · Children · Hypertension · Ambulatory blood pressure monitoring · Steroid

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Introduction

Recent studies have shown that pediatric patients with end stage renal disease (ESRD) suffer from significant cardiovascular morbidity and mortality [1]. The United States Renal Data System study demonstrated that the cardiac deaths rate was 1,000-fold greater in such patients than in the general population [2]. Renal transplantation may reverse some of the cardiovascular risk factors in children with ESRD. However, hypertension (HT) is still a frequent and serious complication in pediatric renal transplant recipients and an important modifiable risk factor that affects graft and patient survival. The most common etiologies of post-transplant HT include immunosuppressive medication (mainly glucocorticoids and calcineurin inhibitors), recipient's native kidneys, graft dysfunction and obesity [3].

In children, 24-h ambulatory blood pressure monitoring (ABPM) becomes more important than the casual blood pressure (BP) for the diagnosis of HT [4]. ABPM enables the BP pattern during an ordinary day to be determined and also measures BP during nighttime. Additionally, ABPM also reveals white-coat HT and enables masked HT, i.e. normal casual BP but increased ambulatory daytime BP, to be diagnosed [5].

Although several studies have been published on the prevalence of post-transplant HT, data on the factors contributing

to this condition are still scarce. The aim of the study was to investigate the prevalence of posttransplant HT and to assess the BP of transplanted children with possible risk factors.

Material and methods

Patients

The inclusion criteria were age between 4 and 18 years, renal transplant performed at least 3 months prior to the beginning of the study and stable graft function (i.e. absence of an increase in serum creatinine of ≥20 % during the last 3 months). A total of 32 patients were followed between 2009 and 2012. Three patients were excluded because of history of renal transplantation within 3 months before study initiation; therefore, 29 children who had undergone renal transplant were included in our analysis. During routine visits by the patients, we collected data on age, gender, height, weight, and body mass index (BMI) after obtaining informed consent. Obesity was defined as a BMI of≥95th percentile and overweight as a BMI of between the 85th and 94th percentile for age and gender. The glomerular filtration rate (GFR) was calculated with the 24-h creatinine clearance. Transplant renal artery stenosis was excluded based on the results of Doppler ultrasonography of the transplant artery. Drug doses of daily immunosuppression and blood levels were documented. The study was approved by the ethical committee of Hacettepe University.

Office BP measurement

After a routine physical examination, office BP was measured by a physician with the appropriate cuff size on the right arm. All office BP measurements were performed after the patient had rested for 1 h, using an Omron® BP monitor (Omron Corp, Kyoto, Japan). The average of three subsequent measurements was used for analysis. For all patients, the 95th percentile of systolic BP (SBP) and diastolic BP (DBP) was evaluated for gender, age and height; the patient was also checked for HT according to the office BP measurement [6].

Ambulatory blood pressure monitoring

All ambulatory BP measurements were performed on an outpatient basis with the same type of the oscillometric device (90217; Spacelabs Healthcare, Snoqualmie, WA). The appropriate cuff size was determined for each patient, and the cuff was placed on the non-dominant arm. The device was set to provide measurements at 20-min intervals during the day and at 30-min intervals during the night. Patients were informed to keep the arm in a resting position during measurements but otherwise to continue normal daily activities. All patients were asked to record their daily activities, including sleep and awakening periods. After 24 h of recording, data were obtained using software from Spacelabs Healthcare. At least 40 valid readings were obtained during the 24-h period and included in the study for analysis. Patients who had regular antihypertensive medication continued using these drug(s) during the study.

Results of the ABPM and office measurements were evaluated for each patient, and necessary dietary and drug interventions were performed to better control the ambulatory BP.

Definitions

Office HT was considered when the patient's SBP and/or DBP was ≥95th percentile for gender, age and height. Ambulatory HT was defined as the SBP and/or DBP at daytime or nighttime, which was the ≥95th percentile of BP for gender and height [7]. HT was regarded either as controlled [defined as normal ambulatory BP measurements of patients on antihypertensive drug(s) which were started before the study either for antiproteinuric or antihypertensive effect] or uncontrolled [defined as ambulatory HT under previous antihypertensive drug(s)] or untreated (defined as ambulatory HT without drugs). Spontaneous normotension was used for the patients who have normal ABPM without any antihypertensive treatment.

The BP standard deviation score (SDS) was calculated for mean SBP and DBP during the daytime and nighttime using the LMS method [8].

Dipping was defined as an approximately 10 % drop in mean SBP and DBP between daytime and the sleep period. Non-dipping was defined as a decline of <10 %.

Data analysis

All statistical analyses were performed using SPSS ver. 15 (SPSS, Chicago, IL). A two-sided p value of <0.05 was considered to be statistically significant. Descriptive statistics for variables were reported as the mean± standard deviation (SD) values for normally distributed data and as the median and total ranges for skewed data. Spearman's rank correlation coefficients were used to investigate the association of DBP and drug dosages.

Results

Patients

Among the 29 patients, 58.6 % were boys (n=17) and 41.4 % were girls (n=12). The age range of the patients was 4.9–17.6 years. Mean and median age at the time of the study were 13.9±2.9 and 14.5 years, respectively. Four patients were underweight (13.8 %). Overweight/obesity was present in

ten patients (34.5 %). More than half of the patients (n=15, 51.7 %) had a normal BMI. The most common primary renal disease was congenital anomaly of the urinary system, such as obstructive uropathy and renal dysplasia. None of the patients experienced recurrence of previous diseases (Table 1).

Previous renal replacement treatment (RRT) was hemodialysis in nine of the patients (31 %), continuous ambulatory peritoneal dialysis in seven of the patients (24.1 %) and concurrent hemodialysis/continuous ambulatory peritoneal dialysis in three patients (10.4 %). Ten patients underwent preemptive transplantation. Mean duration of RRT before transplantation was 21.6±18.1 months. Transplanted kidneys were from living donors in 65.5 % (n=19) of patients. All patients had their first allografts. None of the patients had a history of native kidney nephrectomy. There was no case of allograft renal artery stenosis. Of the 29 patients, five (17.2 %) had experienced a previous acute rejection episode (Table 2). With regards to immunosuppressive regime, 17 patients (58.6 %) were on prednisolone (P)+ mycophenolate mofetil (MMF)/azathioprine (AZA)+ tacrolimus treatment, seven patients were on P+MMF/AZA+cyclosporine A (CsA) treatment and five patients were on an immunosuppressive regime that included both P and sirolimus/everolimus. All of the patients were either on daily doses (n=14) or alternate doses of prednisolone (n=15). In terms of single immunosuppressive drugs, 25 patients used MMF/mycophenolic acid, 18 patients used tacrolimus, seven patients used CsA, five patients used sirolimus/everolimus and two patients used AZA.

Antihypertensive medication was used by 14 (48.2 %) patients during the study period. Most of the patients (n=13, 44.8 %) were being treated with angiotensin-converting enzyme inhibitors (ACEi). There was only one patient treated only with calcium channel blocker (CCB), and one patient was taking both ACEi and CCB (combined therapy). The mean number of antihypertensive drugs per treated patients was 1.07 drugs/patient. None of the patients were using α- or β-blockers for HT. Age, duration of RRT, ABPM or office BP parameters were not different between patients with and without antihypertensive drugs.

Table 1 Etiology of primary renal disease

Primary renal disease	n (%)
Structural malformation (neurogenic bladder, renal agenesis, VUR, PUV, UPJO)	14 (48.3)
Cystinosis/nephronophthisis/amiloidosis secondary to FMF, oligomeganephronia	6 (20.7)
FSGS/RPGN/hereditary nephropathy	5 (17.2)
Unknown	4 (13.8)

VUR, Vesicoureteral reflux; PUV, posterior urethral valve; UPJO, ureteropelvic junction obstruction; FMF, familial Mediterranean fever; FSGS, focal segmental glomerulosclerosis; RPGN, rapidly progressive glomerulonephritis

BP measurements

All patients had both office BP measurements and ABP measurements. Mean office SBP and DBP were 114.7± 12.2 and 76.7±11.0 mmHg, respectively. According to the office BP measurements, three patients had systolic HT, two patients had both systolic and diastolic HT and one patient had diastolic HT; the remaining patients had normal office BP measurements. Based on the office BP measurement, six patients (20.6 %) were hypertensive. All of these hypertensive patients also had abnormal BP results with ABPM. Therefore, no white-coat HT was found among the transplanted children.

All patients had adequate ABPM recordings. During the 24-h monitoring period, the mean SBP and DBP of all patients during the day and night were 119±13.8 and 73.5±11.2 mmHg, respectively.

Based on our evaluation of the overall ABPM results and antihypertensive medication status of the patients, we identified 13 patients (44.8 %) with newly diagnosed untreated HT according to the ABPM results. There were 14 patients (48.2 %) on antihypertensive medication, of whom five had their HT under control. In contrast, the majority of the patients receiving antihypertensive drugs (n=9, 64.2 %) had uncontrolled HT. Only two of the 29 patients had normotension without any antihypertensive drug (Fig. 1). In terms of daytime and/or nighttime, the ABPM revealed HT (untreated and uncontrolled) in 22 of the 29 patients (75.8 %). The ABPM revealed a higher prevalence of HT compared to the office measurements (75.8 vs. 20.6 %, respectively).

During the daytime, seven patients (24.1 %) had systolic and diastolic HT, six patients (20.7 %) had systolic HT and two patients (6.9 %) had diastolic HT; the remaining patients (n=14, 48.2 %) had normal daytime ABP measurements. The prevalence of daytime HT was 51.7 % (n=15). During nighttime, 14 patients (48.3 %) had both systolic and diastolic HT, three patients (10.3 %) had systolic HT and three other patients (10.3 %) had diastolic HT. The prevalence of nocturnal HT was 68.9 %.

In the patient cohort, seven patients (24.1 %) had isolated nocturnal HT and two patients had isolated daytime hypertension. Therefore, 7 % (2/29) had masked HT. Patients with isolated day or nocturnal HT had normal office BP measurements. The remaining patients had HT during both the daytime and nighttime (n=11).

The mean percentage for systolic dipping and diastolic dipping was 7.6±5.5 and 10.7±9.5 %, respectively. Systolic non-dipping and diastolic non-dipping was observed in 16 (55.1 %) and nine (31 %), respectively, of the 29 patients. Systolic or diastolic non-dipping was observed in 19 patients (65.5 %). Inverted systolic dipping was observed in two patients, and inverted diastolic dipping was observed in four patients. One patient had both inverted systolic and diastolic dipping.

The 24-h mean diastolic BP SDS was lower in patients with antihypertensive medication when compared to patients

Table 2 Clinical characteristics, immunosuppressive therapy and ambulatory blood pressure measurements in children at the time of the study

Clinical characteristics, immunosuppressive therapy and ambulatory blood pressure measurements	Mean[a]	Range
Age (years)	13.9 ± 2.9	4.9–17.6
Weight (kg)	43.6 ± 13.8	20–71
Height (cm)	144.7 ± 15.8	103–167
Body mass index (kg/m^2)	20.4 ± 4.04	14.3–26.7
Time after transplantation (months)	24.6 ± 22.2	3–99
Duration of renal replacement therapy (months)	21.6 ± 18.1	3.5–72
Prednisolone dose (mg/kg/day)	0.171 ± 0.125	0.01–0.57
Mycophenolate mofetil dose (mg/m^2/day)	765.2 ± 136.4	520.8–1000
Tacrolimus dose (mg/kg/day)	3.1 ± 1.1	1–5
Tacrolimus through level (mg/ml)	4.3 ± 1.9	0.6–7.3
Cyclosporine A dose (mg/kg/day)	2.4 ± 0.5	1.4–3.0
Cyclosporine A level (2nd hour) (ng/ml)	359.1 ± 248.6	182.6–849.5
Sirolimus dose (mg/kg/day)	1.9 ± 0.8	0.9–3.0
Glomerular filtration rate (ml/min/1.73 m^2)	83.1 ± 30.3	34.7–171.3
Serum creatinine level (mg/dl)	0.92 ± 0.27	0.42–1.45
Daytime systolic blood pressure (SDS)	0.32 ± 1.74	
Daytime diastolic blood pessure (SDS)	0.63 ± 2.11	
Nocturnal systolic blood pressure (SDS)	1.22 ± 1.33	
Nocturnal diastolic blood pressure (SDS)	1.79 ± 1.62	
24-h-systolic blood pressure (SDS)	0.54 ± 1.66	
24-h-diastolic blood pressure (SDS)	1.07 ± 2.06	

SDS, Standard deviation score

[a] Mean is given ± standard deviation (SD) unless indicated otherwise

without treatment, and the difference was statistically significant (p=0.020). Age, duration of RRT, age of the donor, BMI, P, MMF and CsA dosage and drug levels of CsA and tacrolimus were not statistically different between hypertensive (uncontrolled, untreated) and normotensive (controlled, spontaneous) patients. On the other hand, GFR at the time of the study was not significantly different between normotensive and hypertensive patients (p=0.2).

The SDS of the nocturnal diastolic BP of ABPM were positively correlated with the P dosage per kilogram (p=0.013, r=0.45) and negatively correlated with the time period after transplantation (p=0.024, r= −0.41). Similarly, the SDS of the 24-h DBP was positively correlated with the P dosage per kilogram (p=0.006, r=0.50) and negatively correlated with the time period after transplantation (p=0.016, r= −0.44) (Fig. 2a, b). In addition, patients with alternate-day steroid treatment had lower nocturnal systolic (p=0.016), nocturnal diastolic (p=0.001) and 24-h-diastolic (p=0.008) SDS when compared to those receiving daily steroid medication. Daytime systolic, diastolic and 24-h-systolic SDS were not different between patients on alternate-day and daily steroid treatment.

Discussion

The prevalence of post-transplant HT in the pediatric age group is known to be relatively high, ranging from 47 to 82 % [5, 9–13]. In our cross-sectional study, the ABP measurements confirmed that 75.8 % of the post-transplant patients had HT despite the use of antihypertensive drugs by 48 % of the children. Moreover, based on the use of antihypertensive drugs in the definition of HT, the total prevalence of HT was 93 % (27/29). ABPM is reported to be a better tool for the diagnosis of post-transplant HT than office blood measurements [14, 15] and should be routinely performed at regular intervals [16]. The validity of this recommendation is confirmed once again in our study. In our patient group, the

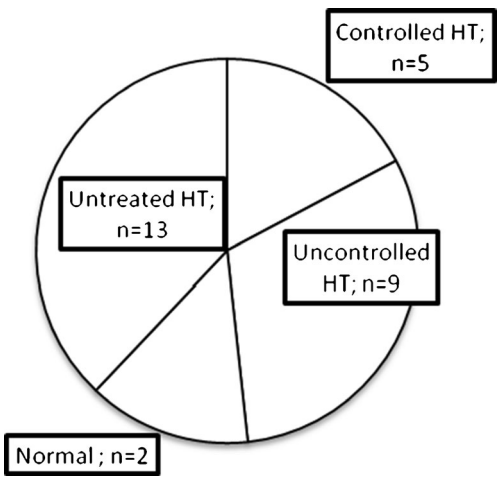

Fig. 1 Patient numbers and the ambulatory blood pressure monitoring results of the whole cohort. *HT* Hypertension

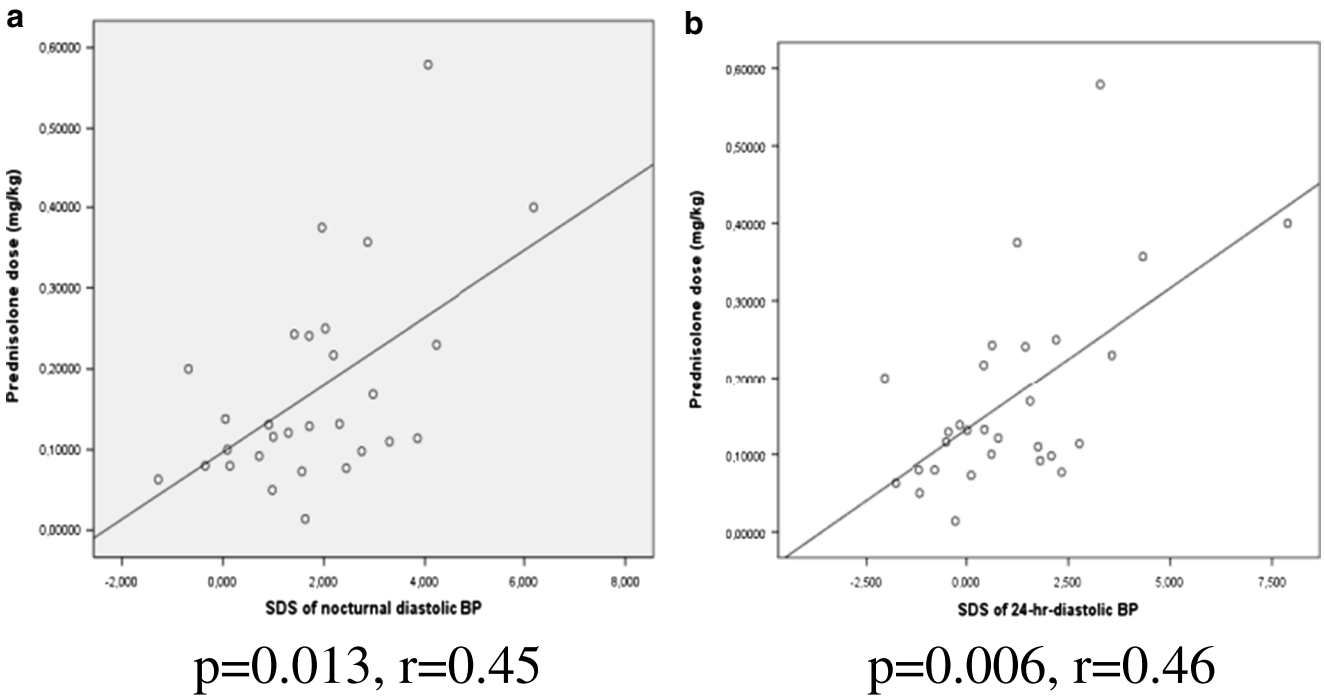

Fig. 2 **a**, **b** Correlations of standard deviation scores (*SDS*) of nocturnal diastolic blood pressure (*BP*) (**a**) and 24-h diastolic BP (**b**) with prednisolone dose (mg/kg)

office BP measurement only diagnosed 20.6 % of the patients as hypertensive. Since these patients also had abnormal ABPM results, this revealed that none of our patients had white-coat HT. Detection of masked HT and isolated nocturnal HT in renal transplant recipients is very important because masked HT is associated with a higher left ventricular mass, and improvement of the BP in this group of patients would increase graft survival [17, 18]. In our patient cohort, the majority of the patients had masked and isolated nocturnal HT. This also indicates the superiority of ABPM in the follow-up of renal transplant recipients.

Another finding of some studies related with HT in kidney transplant recipients has been the absence of isolated daytime HT in these patients. This means when a patient is hypertensive after transplantation, it is either isolated nocturnal HT or combined with daytime HT [10, 19]; whereas, in our study there were only two patients with isolated daytime HT.

Another important aspect is the efficacy of antihypertensive drugs. In other series from different centers, the control rate of HT with medication was 45–58 % [20–22]. Although, nearly half of the patients were on antihypertensive treatment, in our study, in only 36 % of the patients receiving antihypertensive drugs was the HT under control, leading to the suggestion that while most of the patients were correctly diagnosed as hypertensive, they required more than one drug or higher doses. Many different factors, such as immunosuppressive drugs (steroids, CsA, tacrolimus), graft dysfunction, renal graft artery stenosis, post-transplant weight gain and genetic factors contribute to the development of post-transplant HT. Among these factors, the role of immunosuppressive medication is well known. Sodium retention, increase in cardiac output and renal vascular resistance are the main pathophysiological mechanisms [3]. In the study of Sarwal et al. [23], patients with steroid-free immunosuppression had improved HT. In another study, patients with alternate-dose steroid treatment showed a significantly lower prevalence of HT when compared to patients with daily steroid medication [20]. In our study, the prevalence of HT in patients using alternate-dose steroids and daily steroids did not differ. However, patients on alternate-dose steroid had lower SDS in terms of nocturnal systolic, diastolic and 24-h-diastolic BP obtained from the ABPM. Furthermore, the SDS of 24-h DBP was negatively correlated with the duration after renal transplantation. This finding can be explained by the usage of high-dose steroids in the early phase of renal transplantation before the dose was lowered. possibly indicating that alternate-day steroid and/or steroid-free immunosuppression are possible treatment strategies for post-transplant HT.

Attenuation of dipping in renal transplant recipients is another common finding. The average frequency of abnormal systolic dipping has been reported to be almost 78 % [24], and mean nocturnal dipping has been reported to range from 3.2 and 6 % for SBP and between 8.7 % and 13 % for DBP [5, 9, 24, 25]. The rate of systolic dipping of our patients was higher than has previously been reported.

In conclusion, our results suggest that HT is an important problem in kidney transplant recipients. After renal transplantation, follow-up with ABPM is of utmost importance because

this method provides more valuable information on the BP of the patients than office BP measurements. The daily prednisolone dose had an impact on diastolic BP. Based on our results, we recommend alternate-day steroid regimes. Due to the multidimensional nature of the subject, regular ABPM will help to determine the best follow-up strategy in this group of patients.

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