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Original Article

Albuminuria is associated with 24-hour and night-time diastolic blood pressure in urinary tract infection with renal scarring

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ABSTRACT

Background. We aimed to detect complications and associated risk factors in patients with renal scarring (RS) secondary to recurrent urinary tract infections (UTI).

Methods. Fifty patients with RS were compared with 25 patients without RS by means of, serum creatinine, 24-hour urinary creatinine clearance, and 24-hour urinary albumin levels. Office blood pressure (BP) examination and ambulatory BP monitoring (ABPM) were also performed.

Results. Vesicoureteral reflux was detected in 50 patients. Glomerular filtration rate (GFR) <90 ml/min/1.73 m2 was observed in 5 patients with RS but in no patient without RS. Albuminuria was significantly higher in patients with bilateral RS and severe RS. Patients with albuminuria had a significantly lower GFR than those without. All patients with ambulatory hypertension (HT) were in the RS group, and 60% of those had isolated nocturnal HT. Compared to those without RS, patients with RS had significantly higher SDS values for all BP readings, 24-hour and nighttime systolic and diastolic BP loads with significantly lower systolic dipping. GFR was negatively correlated with diastolic BP SDS and diastolic BP load in patients with RS. Daytime diastolic BP load was significantly higher in those with severe RS than in those with mild RS.

Conclusions. Isolated nocturnal HT could be an early sign of complications in RS of UTI. Albuminuria is related to increased BP and impaired renal function. Therefore, ABPM and assessing albuminuria should be a routine part of the follow-up. Diastolic BP elevations could be associated with worse outcomes in these patients.

Key words: albuminuria, ambulatory blood pressure monitoring, hypertension, renal scarring.

Urinary tract infection (UTI) is the most common bacterial infection in children after otitis media and is one of the major causes of acquired renal scarring (RS). Febrile UTIs associated with renal parenchymal inflammation may lead to nephron injury, resulting in permanent RS.[1]

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The incidence of developing permanent RS after UTI ranges from 15 to 60%, depending on factors such as age and sex of the patient, diagnostic criteria for UTI, reflux grade, and genetic susceptibility.[2]

Long-term complications of RS include hypertension (HT), proteinuria, impaired renal function, growth retardation, and problems during pregnancy.[3] However, the prevalence and onset of these problems are not fully understood, because they have an insidious onset and require long-term follow-up. Hypertension as a consequence of RS results in progressive renal dysfunction. Without early detection and timely control, HT accelerates the development

of end-stage kidney disease (ESKD). Therefore, close blood pressure (BP) monitoring is essential in patients with RS. Ambulatory blood pressure monitoring (ABPM) is superior to office BP measurement for detecting HT due to many factors such as obtaining multiple BP readings compared to a single measurement, eliminating BP measurement errors, and availability of daytime and nighttime BP measurements.[4] Some cases with RS have been diagnosed as hypertensive with ABPM, although office BP is normal.[5]

In the present study, we aimed to detect long-term complications of RS, identify the predictors of renal dysfunctions, evaluate the presence of HT by using ABPM and determine the effect of HT and albuminuria on progression.

Material and Methods

Patients

In this cross-sectional study, 75 patients who were older than five years of age and followed up for recurrent UTI at Hacettepe University Faculty of Medicine were included. Recurrent UTI was defined as two discrete febrile UTI episodes with positive urine cultures during a 12-month follow-up period. Patients with obstruction in the urinary tract, history of medication, and chronic disorders that could affect BP were excluded.

All patients that were regularly followed up were evaluated at the last follow-up visit. Age, sex, anthropometric, and office BP measurements were recorded. Height and body mass index (BMI) z-scores were calculated using the World Health Organization (WHO) Anthro-plus software. Serum creatinine, blood urea nitrogen (BUN), 24-hour urinary creatinine, and 24-hour urinary albumin levels were measured. Glomerular filtration rate (GFR) was calculated as creatinine clearance in 24-hour urine. Urinary albumin excretion greater than 30 mg/day was considered as albuminuria.

Blood pressure

At the last visit, office BP measurement was performed for each patient using the auscultation method by a physician with the appropriate cuff size on the right arm after a minimum rest of 20 minutes. The results were evaluated according to the European Society of Hypertension guidelines.[6]

A 24-hour ABPM was performed with the AccuWin Pro v3 device (SunTech Medical, Inc., Morrisville, NC). The cuff of the device was placed on the non-dominant arm of the patient using an appropriately sized cuff. All patients were asked about their daily activities and sleep and awake periods, and these periods were recorded as daytime and nighttime. The devices were programmed to measure BP every 20 min during the daytime and every 30 min at nighttime. ABPM was standardized using the method of least median of squares, and BP percentiles were evaluated according to Wühl et al.'s reference values by patient sex and height.[7] Ambulatory HT was defined as a mean systolic and/or diastolic BP ≥95th percentile and systolic and/or diastolic BP load ≥25% for either the wake or sleep period of the study, or both. Ambulatory prehypertension was defined as a mean systolic and/or diastolic BP <95th percentile, but systolic and/or diastolic BP load ≥25% for either the wake or sleep period of the study, or both.[8] A blood pressure drop by at least 10% at night compared to daytime BP was defined as "dipping", and the absence of such a drop was defined as "non-dipping".

Imaging studies

Vesicoureteral reflux (VUR) was assessed by voiding cystourethrography (VCUG) results. VUR was graded using 5 grades according to the International Reflux Study Standardization in Children.[9] The patients were grouped according to the VUR grade so that those with grade I and II VUR were in Group A, those with grade III in Group B, and those with grade IV and V in Group C. Patients with bilateral VUR, the grade was described as major reflux status.[10]

Diagnosis of RS was based on Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy results, which were already available for the patients. Fifty patients had RS, and 25 patients did not have RS. Fifty patients with RS in two different scintigraphies at least 6 months apart were deemed to have permanent RS. All DMSA scintigraphies were re-evaluated by a nuclear medicine specialist by dividing the renal cortical area into 12 segments, with renal involvement categorized as mild scarring when 1-2 segments were affected, moderate scarring when 3-4 segments were affected, and severe scarring when more than 4 segments were affected. Patients with bilateral scarring were similarly categorized by the total scar area.[11,12]

Statistical analysis

Statistical analyses were performed with SPSS version 24 (IBM Corp. Armonk, NY). Descriptive statistics included mean, standard deviation, minimum, maximum, median, and frequency values. Data distribution was tested using the Kolmogorov–Smirnov test. Quantitative data were analyzed using t-test and ANOVA test for parametric variables and Mann Whitney-U test and Kruskal-Wallis test for non-parametric variables. Qualitative variables were compared using the Chi-square test; when test assumptions were not met, Fisher's exact test was used. Correlation analyses were carried out using Pearson and Spearman correlation analyses. The study was approved by the Ethics Committee of Hacettepe University. Informed consent was obtained before enrollment.

Results

Patient characteristics

A total of 75 patients (63 females, 12 males) were enrolled in the study. Among them, 50 patients had RS, and 25 patients did not have RS. Among patients with RS, 27 (54%) patients had mild, 10 (20%) had moderate, and 13 (26%) had severe RS. Forty-four (88%) patients had unilateral RS, and six (12%) had bilateral RS. The mean duration from the first UTI to the last visit was 9.7±3.8 years for patients with RS and 8.2±3 years for those without RS (p=0.09). There was no significant difference between patients with and without RS regarding age, sex, duration of follow-up, height z-score, and BMI z-score (Table I).

Fifty (66.7%) patients had VUR, which was classified into three categories: groups A, B, and C. Thirty-four (68%) patients had unilateral VUR, and 16 (32%) had bilateral VUR. RS rate was higher in patients with bilateral VUR than patients with unilateral VUR, but it was not statistically significant (p=0.60). There was a correlation between VUR grade and RS severity (r=0.45, p=0.01) (Supplementary Table I).

Glomerular filtration rate at last visit

At the last visit, in the RS group, the mean GFR was 123.7±33.0 ml/min/1.73 m^2, while in patients without RS, the mean GFR was 128.5±22.6 ml/min/1.73 m^2 (p=0.51). Similarly, GFR values did not significantly differ between patients with unilateral versus bilateral RS and between patients with mild, moderate, and

Table I. Demographic and clinical characteristics of the patients.

Parameters	RS (+), n=50	RS (-), n=25	p
Sex (female/male), n/n	41/9	22/3	0.50
Duration of follow-up (years)	9.7 ± 3.8	8.20 ± 2.95	0.09
Age at last visit (years)	12.6 ± 3.4	11 ± 3.46	0.06
BMI-z score at last visit	0.6 ± 1.2	0.5 ± 1.5	0.79
Height z-score at last visit	0.2 ± 1.1	0.6 ± 1.2	0.80

Data are presented as mean ± standard deviation
BMI: body mass index, RS: renal scarring

severe RS (p=0.32, p=0.50, respectively). The RS group included five patients with a GFR <90 ml/min/1.73 m^2, while the group without RS had no patient with a GFR <90 ml/min/1.73 m^2. In patients with RS, the mean duration of follow-up of the patients with GFR <90 ml/min/1.73 m^2 and >90 ml/min/1.73 m^2 was 13.06±1.71 years and 9.31±3.65 years, respectively (p=0.03).

Proteinuria

At the last visit, 24-hour urinary albumin levels were measured in all patients except two patients with RS due to noncompliant issues. The median albumin excretion was 6.7 (IQR, 0.9-14.2) mg/day in the RS group and 5.5 (IQR, 3.4-8.0) mg/day in the non-RS group (p=0.40). In 24-hour urine, albuminuria was detected in seven (14.5%) patients with RS (six patients; 30-300 mg/day, one patient; >300 mg/day), while there was no patient with albuminuria in the non-RS group. The 24-hour albumin excretion was significantly higher in patients with severe RS than in patients with mild RS (p=0.04) (Fig. 1). Similarly, there was a correlation between 24-hour urinary albumin level and RS severity (Spearman correlation, r=0.334, p=0.02).

The median 24-hour urinary albumin was 4.1 (IQR, 0.0-12.1) mg/day in patients with unilateral RS and 27.1 (IQR, 10.6-108.8) mg/day in patients with bilateral RS (p=0.01). In patients with RS, 9.5% of patients with unilateral RS had albuminuria, while 50% of patients with bilateral RS had albuminuria. As a result, albuminuria incidence was significantly higher in patients with bilateral RS compared to patients with unilateral RS (p=0.01).

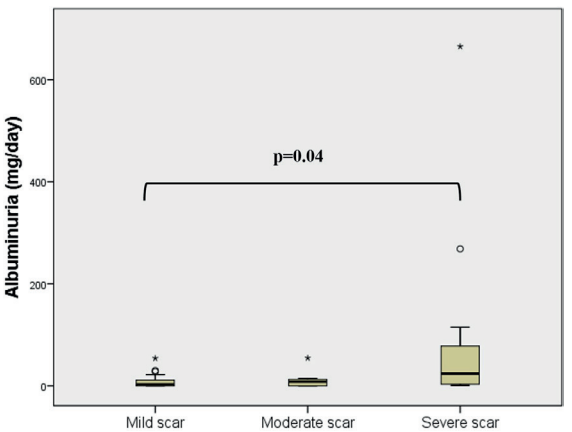

Fig. 1. Comparison of 24-hour urinary albumin level according to renal scarring severity.

The mean GFR of the patients with albuminuria and RS was 85.8 ± 37.1 ml/min/1.73 m^2, while the mean GFR of RS patients without albuminuria was 129.1 ± 28.7 ml/min/1.73 m^2 (p=0.001).

Blood pressure

According to office BP measurements, among patients with RS, 9 (18%) out of 50 patients had high-normal BP, and 9 (18%) had HT. On the other hand, in the group without RS, HT was detected in only one patient (4%).

ABPM was performed in 73 patients (one patient with RS and the other without RS did not give informed consent). Of 55 patients with normal office BP measurements, 44 (80.4%) had normal ABPM, 9 had ambulatory prehypertension, and 2 had ambulatory hypertension (Supplementary Table II).

Ambulatory prehypertension was found in eight (16.3%) patients with RS and in four (16.6%) patients without RS. Ambulatory HT was found in 10 (20.4%) patients with RS. Ambulatory HT was not found in any patient without RS. Out of 10 patients with RS and ambulatory HT, six (60%) had isolated nocturnal BP elevation and normal daytime BP readings, while four (40%) had daytime and nighttime HT. Similarly, six (75%) of eight patients with ambulatory prehypertension and RS had an isolated nocturnal BP load ≥25% with daytime BP load <25% and two of them had daytime and nighttime blood pressure load ≥25%.

According to ABPM results, 24-hour systolic BP standard deviation scores (SDS), 24-hour diastolic BP SDS, daytime systolic BP SDS, daytime diastolic BP SDS, nighttime systolic BP SDS, nighttime diastolic BP SDS, 24-hour MAP SDS, daytime MAP SDS, and nighttime MAP SDS values were significantly higher in patients with RS than in those without. 24-hour systolic

Table II. Comparison of blood pressure standard deviation scores, blood pressure load, and dipping values in patients with and without renal scarring.

Parameters	RS (-), n=24	RS (+), n=49	p
24-hour SBP SDS†	-0.92 ± 1.15	-0.01 ± 1.25	0.03
24-hour DBP SDS‡	-1.39 (-3.66-0.90)	-0.84 (-3.01-3.71)	0.02
24-hour MAP SDS†	-0.90 ± 0.98	-0.15 ± 1.25	0.01
Daytime SBP SDS†	-0.94 ± 1.09	-0.26 ± 1.23	0.02
Daytime DBP SDS‡	-1.67 (-3.36-0.93)	-1.29 (-2.53-3.06)	0.03
Daytime MAP SDS‡	-1.16 (-2.85-0.79)	-0.74 (-1.90-3.55)	0.02
Nighttime SBP SDS†	-0.40 ± 0.91	0.59 ± 1.06	<0.001
Nighttime DBP SDS†	-0.38 ± 0.84	0.32 ± 1.06	0.01
Nighttime MAP SDS†	-0.32 ± 0.78	0.49 ± 1.10	0.002
24-hour SBP load (%)‡	6.5 (0-21)	10 (0-82)	0.02
24-hour DBP load (%)‡	2.5 (0-21)	6 (0-90)	0.02
Daytime SBP load (%)‡	6.5 (0-23)	8 (0-77)	0.17
Daytime DBP load (%)‡	1 (0-28)	4 (0-86.7)	0.13
Nighttime SBP load (%)‡	0 (0-29)	17 (0-92)	<0.001
Nighttime DBP load (%)‡	0 (0-30)	11.1 (0-100)	0.002
Systolic dipping (%)†	10.86 ± 3.98	8.27 ± 3.98	0.01
Diastolic dipping (%)†	15.88 ± 6.33	13.79 ± 6.30	0.19

†Mean ± standard deviation, ‡median (range).
SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, RS: renal scarring, SDS: standard deviation score

BP load, 24-hour diastolic BP load, nighttime systolic BP load, and nighttime diastolic BP load were significantly higher in patients with RS than in those without. Furthermore, patients with RS had significantly lower systolic BP dipping than patients without RS (Table II). In addition, when the difference between daytime and nighttime blood pressure SDS and blood pressure loads in patients with RS was evaluated; nighttime systolic blood pressure SDS was significantly higher than daytime systolic blood pressure SDS, nighttime diastolic blood pressure SDS was significantly higher than daytime diastolic blood pressure SDS, and nighttime MAP SDS was significantly higher than daytime MAP SDS (p=<0.001, p=<0.001, p=<0.001 respectively). Similarly, nighttime SBP load was significantly higher than daytime SBP load and nighttime diastolic BP load was significantly higher than daytime diastolic BP load in patients with RS (p=<0.001, p=<0.001 respectively).

According to RS severity, daytime diastolic BP load was significantly higher in the severe RS group than in the mild RS group (median: 7.5; range: 0.0-86.7 versus median: 3.0; range: 0.0-46.8, p=0.01). Other BP loads, BP SDS values, and dipping values were not significantly different according to RS severity.

Among patients with RS, 24-hour diastolic BP SDS and nighttime diastolic BP SDS values were significantly higher in patients with albuminuria than in those without (Table III) (p=0.035, p=0.02).

A significant negative correlation was found between GFR and 24-hour diastolic BP SDS (p=0.005, r=-0.47), nighttime diastolic BP SDS (p= 0.036, r=-0.34), 24-hour MAP SDS (p= 0.033, r=-0.28), 24-hour diastolic BP load (p= 0.020, r=-0.32), and nighttime diastolic BP load (p= 0.030, r=-0.29) in patients with RS (Fig.2).

Table III. Comparison of blood pressure standard deviation scores of patients with and without albuminuria among patients with renal scar.

Variables	Blood pressure	Albuminuria <30 mg/day, n=40	Albuminuria >30 mg/day, n=7	p
24-hour	Systolic SDS[a]	-0.02 ± 1.19	-0.27 ± 1.59	0.62
	Diastolic SDS[b]	-1.04 (-3.01/1.83)	-0.62 (-0.84/3.71)	0.04
	MAP SDS[b]	-0.37 (-2.18/2.57)	-0.29 (-1.02/4.47)	0.49
Daytime	Systolic SDS[a]	-0.25 ± 1.18	-0.59 ± 1.57	0.50
	Diastolic SDS[b]	-1.44 (-2.5/1.80)	-0.60 (-1.69/3.06)	0.11
	MAP SDS[b]	-0.80 (-1.9/2.50)	-0.47 (-1.66/3.55)	0.63
Nighttime	Systolic SDS[a]	0.54 ±1.04	0.57 ± 1.21	0.93
	Diastolic SDS[b]	0.10 ± 0.94	1.12 ± 1.28	0.02
	MAP SDS[a]	0.32 ± 0.95	0.98 ± 1.50	0.13

[a]Mean ± standard deviation, [b]median (range). MAP: mean arterial pressure, SDS: standard deviation score.

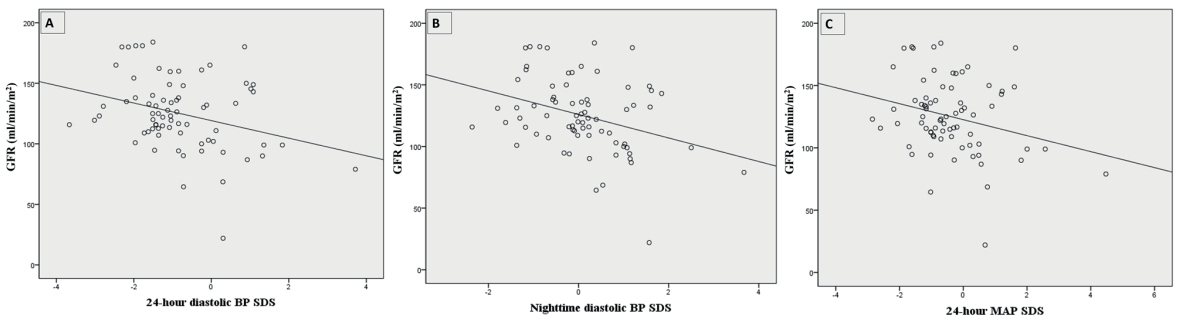

Fig. 2. Correlation between glomerular filtration rate (GFR) and (A) 24-hour diastolic blood pressure (BP) standard deviation score (SDS), (B) nighttime diastolic BP SDS, (C) 24-hour mean arterial pressure (MAP) SDS among patients with renal scarring (p=0.005, 0.036, 0.033, r= -0.37, -0.34, -0.28, respectively).

Discussion

In this study, we investigated long-term complications of RS in a pediatric cohort. 24-hour urinary albumin level was higher in patients with severe and bilateral RS. In addition, the GFR of patients with albuminuria was significantly lower than those without. These results suggest that albuminuria is a risk factor for progression. Furthermore, in patients with RS, 6 out of 10 patients with ambulatory hypertension and, 6 out of 8 patients with ambulatory prehypertension had isolated elevated nocturnal blood pressure. The fact that this situation can only be detected with ABPM highlights the importance of using ABPM in routine care. Another important finding of this study is GFR was negatively correlated with diastolic BP in patients with RS. These results suggest that diastolic blood pressure elevation and isolated nocturnal blood pressure elevation may be early signs of sustained hypertension and progression.

The incidence of chronic kidney disease (CKD) and ESKD is highly variable among patients with RS secondary to pyelonephritis. Gebäck et al.[13] examined 86 patients with a median age of 41 years who had UTI in childhood and reported one patient with stage 3 CKD, 14 patients with stage 2 CKD, and 43 patients with stage 1 CKD and that patients with bilateral RS had significantly lower GFR. Patzer et al.[14] examined 61 patients aged 5-18 years with a history of recurrent febrile UTI and RS, without obstructive uropathies. They found that nine

patients had GFR <90 ml/min/1.73 m^2, and two had GFR ≤50 ml/min/1.73 m^2. Our study detected five patients with RS who had a GFR lower than 90 ml/min/1.73 m^2. The duration of follow-up of the patients with GFR <90 ml/min/1.73 m^2 was longer than those with GFR >90 ml/min/1.73 m^2. This shows the detrimental effect of RS on GFR, especially over time.

Despite the relationship between HT and RS being well known, its incidence and risk factors are not clear. Although the likelihood of RS causing HT is better understood in adulthood, there is a need for additional studies on its incidence and time of onset in children.[15] Although office BP measurement is easy and cheap, ABPM was shown to be more specific for the diagnosis of HT.[16] Fidan et al.[17] monitored 240 patients with VUR and a mean age of 7.1 years for 24 months. They found that although office BP was normal, 17 patients were diagnosed with HT using ABPM. Patzer et al.[14] studied 61 patients with RS secondary to UTI and diagnosed HT in 17 (28%) patients using ABPM and in 24 (39%) patients using office BP measurements. In our study, 49 patients with RS underwent ABPM, ten (20.4%) of these patients had ambulatory HT, and eight (16.3%) had ambulatory prehypertension. Seven of the patients with RS had no HT on office BP, three had ambulatory HT, and four had ambulatory prehypertension with ABPM. These results indicate that in patients with RS, ABPM should be a part of routine care, especially for the detection of masked hypertension.

Furthermore, in patients with RS, six out of ten (60%) patients with ambulatory HT had isolated nocturnal HT, while of six out of eight (75%) patients with ambulatory prehypertension had isolated nocturnal BP elevation, indicating that these patients have a high rate of nocturnal BP elevation. When daytime and nighttime blood pressure SDS and blood pressure loads were compared in patients with RS, nighttime values were found to be significantly higher than daytime. Blood pressure varies according to the circadian rhythm, which is associated with the sympathetic nervous system and renin-angiotensin systems. Previous studies have shown that nocturnal hypertension is associated with end-organ injury and poor prognosis in patients with diabetes, CKD, and organ transplant recipients in adults and children.[18-24] Data from the Cardiovascular Comorbidity in Children with Chronic Kidney Disease Study (4 C) established significant associations between nighttime HT and left ventricular hypertrophy, elevated cIMT and elevated pulse wave velocity.[25] Besides all these, there are few data about nocturnal hypertension in patients with RS.[14] According to our data, HT in children with RS is mostly seen as isolated nocturnal HT. Because isolated nocturnal HT may be an early finding of sustained HT, early detection and treatment of this situation would be vital in terms of good prognosis.

In adults, the relationship between microalbuminuria and progressive renal failure and cardiovascular risk is well known.[26-28] However, there are a few studies on this topic in children. Although hyperfiltration in the remaining nephrons and glomerulosclerosis is thought to cause microalbuminuria in patients with RS, microalbuminuria itself also has nephrotoxic effects. Studies in children with RS have shown that microalbuminuria is associated with lower GFR and severe and bilateral RS.[29,30] Our study also demonstrated that 24-hour albumin excretion was significantly higher in patients with severe RS and bilateral RS. Patients with RS and albuminuria had lower GFR and higher BP readings than that patients without albuminuria. These results indicated that patients with albuminuria were in the high-risk group, had worse ABPM readings, and lower renal function, suggesting that albuminuria should be sought in the routine follow-up of these patients. When it is detected, they should be considered in the risk group for BP elevation and impaired renal function.

Diastolic hypertension is not a well-known entity. However, several studies have found that diastolic BP elevations in childhood are associated with secondary HT.[31,32] Studies have revealed that isolated diastolic HT is

rare but independently affects the risk of adverse cardiovascular events in adults.[33,34] Conversely, isolated diastolic HT was not found to be significantly associated with increased cardiovascular risk in another study.[35] There is insufficient data on the importance of diastolic HT in patients with RS. In this study, a higher diastolic BP was found in the risk group with albuminuria and low GFR, suggesting that diastolic BP elevations may be an early sign of sustained HT and poor prognoses.

There are several limitations in our study, such as the relatively small number of patients and the inability to compare ABPM results with end-organ damage findings such as cIMT and left ventricular hypertrophy. On the other hand, the relatively long follow-up period and the evaluation of BP with ABPM are the strengths of the study.

In conclusion, early detection of RS-associated HT and microalbuminuria is a crucial step for preventing progression to renal failure. There was a negative correlation between GFR and diastolic BP in patients with RS. Isolated nocturnal BP elevation may be one of the earliest signs during the follow-up of these patients. Therefore, these patients should be evaluated by ABPM intermittently.

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Ethical approval

Approval was obtained from the Non-Interventional Clinical Researches Ethics Board of Hacettepe University (28th February 2017, GO 17/94-08). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Author contribution

The authors confirm contribution to the paper as follows: All authors contributed to the study conception and design. Data collection and analysis: DB and RT, draft manuscript preparation: DB; and all authors commented on previous versions of the manuscript and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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