

## ORIGINAL ARTICLE

# Renal histopathological findings in relation to ambulatory blood pressure in chronic kidney disease patients

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Recent studies have demonstrated that ambulatory blood pressure monitoring is useful for predicting the long-term renal prognosis and future cardiovascular events in chronic kidney disease patients. Currently, however, information is limited regarding the relationships between individual renal histopathological findings and abnormalities in ambulatory blood pressure. This retrospective cross-sectional study included a total of 138 patients, in whom both renal biopsies and ambulatory blood pressure monitoring were performed during the same admission period. Renal histopathological findings, including global glomerulosclerosis, interstitial fibrosis/tubular atrophy and the presence of arterial lesions and arteriole lesions, were scored and analyzed in relation to the ambulatory blood pressure values. Among these histopathological characteristics, only the severity of interstitial fibrosis/tubular atrophy exhibited a significant association with an increased mean value of daytime and nighttime blood pressure. However, the remaining histopathological features showed only trends or weak relationships with these values. In addition, a moderately advanced grade of interstitial fibrosis/tubular atrophy was found to be significantly associated with both daytime and nighttime hypertension, independent of the kidney function, overt proteinuria and the use of antihypertensive medications, according to multivariate analyses. Furthermore, the night-to-day ratio of the mean blood pressure displayed a significant increasing trend according to the grade of interstitial fibrosis/tubular atrophy. These results suggest that interstitial fibrosis/tubular atrophy is the most relevant renal histopathological parameter associated with abnormalities in ambulatory blood pressure, including nocturnal hypertension, in this population.

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**Keywords:** ambulatory blood pressure monitoring; chronic kidney disease; interstitial fibrosis/tubular atrophy; nocturnal hypertension; renal biopsy

## INTRODUCTION

Hypertension is a principal cause of chronic kidney disease (CKD) and an exacerbating factor of preexisting CKD. In fact, hypertension is found in at least 70% of patients with CKD.<sup>1</sup> In particular, nocturnal hypertension is often observed with ambulatory blood pressure monitoring (ABPM) in CKD patients.<sup>2,3</sup> In addition, it has been reported that the detection of nocturnal hypertension in patients with ABPM is a useful finding for predicting a poor renal prognosis and future cardiovascular events in such patients.<sup>4,5</sup> Therefore, ABPM may be more useful than office or home blood pressure (BP) measurement in the management of BP abnormalities in CKD patients. In another cross-sectional study, the s.d. of the daytime BP in the ABPM was strongly correlated with the renal vascular resistance assessed by renal Doppler ultrasonography in hypertensive patients. Thus, ABPM is a more efficacious index for evaluating very early renal damage than the estimated glomerular filtration rate (eGFR).<sup>6,7</sup>

Hypertension in the setting of CKD is caused by various factors, including salt sensitivity and increased activity of the renin–angiotensin and sympathetic nervous systems.<sup>8,9</sup> Importantly, most factors related to the pathogenesis of hypertension are also associated with renal tissue injury, suggesting that the factors contributing to both BP abnormalities and renal tissue injury share similar pathophysiological mechanisms. Currently, however, little is known regarding the relationships between renal histopathological findings and BP abnormalities, including those analyzed using ABPM in CKD patients. In the current study, therefore, we aimed to determine the relationships between individual renal histopathological parameters and ABPM findings in CKD patients treated with renal biopsies. Investigating the renal histopathological findings associated with abnormalities in the ABPM may help identify the lesions responsible for BP regulation within the injured kidneys in CKD patients.

## METHODS

### Settings and participants

This retrospective cross-sectional study included consecutive patients who underwent percutaneous native renal biopsies and ABPM at the Jikei University Hospital, Tokyo, Japan, during the period from April 2010 to March 2013. Patients with acute kidney injury, nephrotic syndrome and rapidly progressive glomerulonephritis were excluded from the analysis. Both the renal biopsies and ABPM were performed during the same hospitalization period. The patients' sodium intake (6 g per day) was restricted during hospitalization. Diabetes mellitus was defined as a value of HbA1c >6.5% (National Glycohemoglobin Standardization Program (NGSP)) or as patients under medical treatment for diabetes mellitus at the time of renal biopsy. The eGFR was calculated by applying a modified three-variable equation for estimating the GFR for Japanese patients:<sup>10</sup>  $eGFR = 194 \times \text{Age}^{-0.287} \times s\text{-Cr}^{-1.094}$  ( $\times 0.739$ , if female), where s-Cr is the serum creatinine. All patients included in this study provided their written informed consent for the renal biopsy. The study protocol was approved by the ethics review board of the Jikei University School of Medicine (24-317 7083).

### ABPM analysis

ABPM was performed when possible in all CKD patients with or without hypertension 4–7 days after admission and 2–5 days after the renal biopsy to evaluate the circadian BP and the possible risk of future progression to renal failure. The ABPM analyses were performed using a TM-2431C (A&D, Tokyo, Japan) device. The bladder size of the device was 22 cm  $\times$  12 cm. The BP was measured every 30 min during the day and every 60 min at night. We defined the BP parameters according to the Japanese Society of Hypertension guidelines as follows: (i) daytime and nighttime BP were defined as the mean value of the daytime and nighttime BP, respectively; (ii) daytime hypertension was defined as a daytime BP of >135 mm Hg for systolic BP and >85 mm Hg for diastolic BP, and nighttime hypertension was defined as a nighttime BP of >120 mm Hg for systolic BP and >70 mm Hg for diastolic BP; (iii) the night-to-day ratio (NDR) was defined as the ratio of the nighttime mean BP to the daytime mean BP,<sup>11</sup> and NDR of 0.9 was used as a threshold to distinguish a nondipper and dipper pattern of the circadian rhythm of BP.<sup>12</sup> The change in the nocturnal BP was calculated as  $100 \times (1 - \text{NDR})$ . A dipping status regarding the BP was defined as follows: extreme dipper = the decrease in nocturnal BP was  $\geq 20\%$ ; dipper = a decrease in nocturnal BP of  $\geq 10\%$  and <20%; nondipper = a decrease in nocturnal BP of >0 and <10%; and reverse dipper = a decrease in nocturnal BP of <0%.<sup>12</sup>

### Histopathological analysis

All renal tissue specimens were obtained via percutaneous needle biopsies. The tissues were embedded in paraffin, cut into 3- to 4- $\mu\text{m}$  sections and stained with hematoxylin–eosin, periodic acid–Schiff, Masson's trichrome and periodic acid–methenamine silver stain. Biopsies containing <5 glomeruli were regarded to be inadequate for scoring and were excluded from the analysis. Four candidate chronic renal histopathological findings, including global glomerulosclerosis (GS), interstitial fibrosis/tubular atrophy (IF/TA) and the presence of arterial lesions (AA) and arteriole lesions (AO), were evaluated. The histopathological findings were independently evaluated by two well-trained nephrologists (KH and NT). The patients' information was blinded at the time of the histopathological evaluation, and the identified values were averaged before grading. Representative photomicrographs of each histological grade are presented in Figure 1. The histopathological grading of the four parameters was performed according to the definitions of the Oxford classification, as originally proposed for the evaluation of IgA nephropathy.<sup>13</sup> The grade of GS was defined based on the ratio of the number of sites of GS to the total number of glomeruli identified on the biopsy specimen, as follows: grade 0 = <5%, grade 1 = 5–25% and grade 2 = >25%. The grade of IF/TA was evaluated according to semiquantitative methods. We defined a severity of IF/TA of <5% as grade 0, 5–25% as grade 1 and >25% as grade 2. The grade of AA was scored according to the most severe lesions, and intimal thickening was scored by comparing the thickness of the intima to that of the media in the same segment of the vessel. We defined a severity of AA involving the absence of

intimal thickening as grade 0, 50% or less as grade 1 and >50% as grade 2. The grade of AO was evaluated based on the proportion of arteriolar arteries exhibiting hyalinosis as follows: grade 0 = a proportion of lesions of <5%, grade 1 = a proportion of lesions of 5–25% and grade 2 = a proportion of lesions of >25%.

### Statistical analysis

A one-way analysis of variance was used to analyze the trends in the mean BP values in relation to each histopathological finding. A Kruskal–Wallis analysis was used to compare the prevalence of daytime and nighttime hypertension, and a frequency of NDR of >0.9 for each histopathological grade. Univariate and multivariate logistic analyses were applied to identify the factors associated with daytime and nighttime hypertension. The relevant parameters or the variables that were significantly associated on the basis of a univariate analysis were included in the multivariate analysis. The data were analyzed using a commercially available software program (SPSS version 16.0, Chicago, IL, USA). Values of  $P < 0.05$  were considered to be significant in all statistical tests.

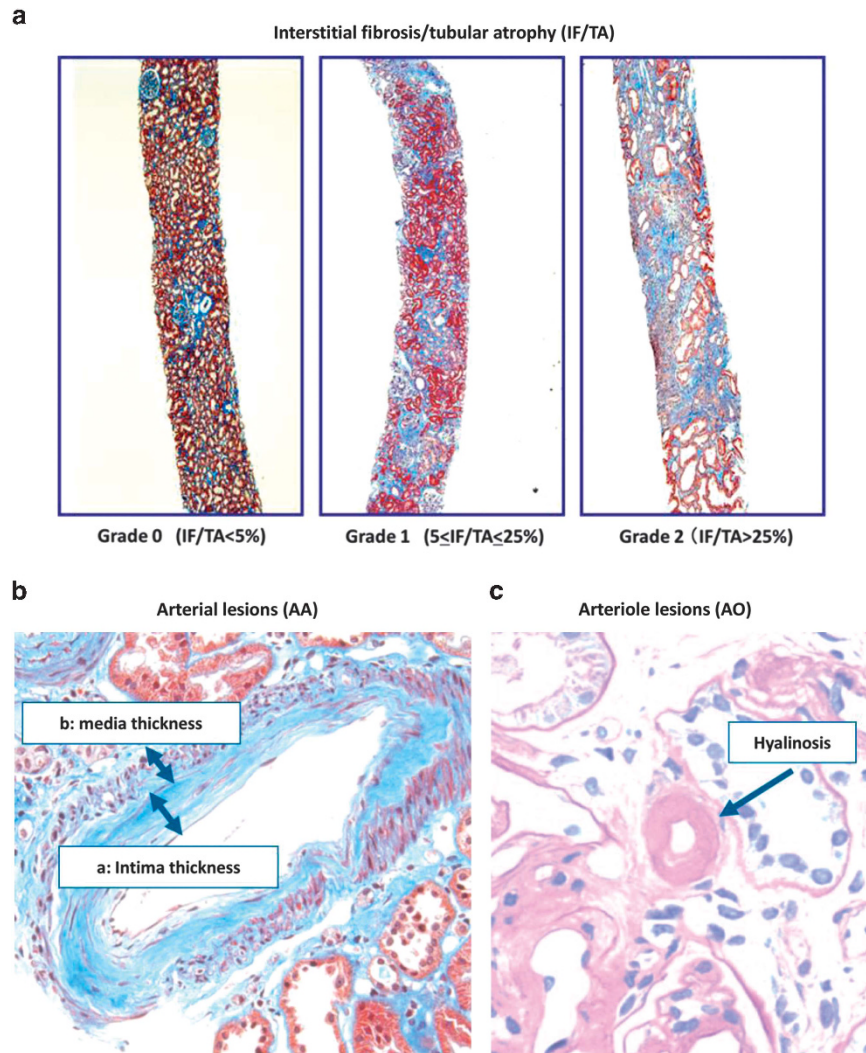
## RESULTS

### Clinical characteristics of the subjects at the time of the biopsy

We initially enrolled 256 consecutive patients who underwent a native renal biopsy. Patients were excluded if they had acute kidney injury or rapidly progressive glomerulonephritis ( $n = 36$ ), nephrotic syndrome ( $n = 50$ ) or an inadequate renal biopsy specimen of fewer than five glomeruli ( $n = 2$ ). Among the remaining 168 patients, 138 patients (82%) received ABPM. The clinicopathological characteristics of the 30 patients who did not receive ABPM were similar to the 138 patients included in this study, except that the 30 patients without ABPM had lower eGFRs at the time of biopsy. The clinical characteristics of the subjects at the time of the biopsy are summarized in Table 1. Approximately half of the patients had a GFR category of 1 or 2, and the other half had a GFR category of 3a, 3b, 4 or 5. The mean amount of urinary protein excretion of the patients was 1.24 g per day. Almost half of the patients received antihypertensive medications. Thirty-nine percent of the patients in the study received angiotensin-converting enzyme inhibitors or angiotensin type-1 receptor blockers, 11% of whom also received diuretics. The distribution of the histological diagnosis was as follows: 73 (53%) patients were diagnosed with IgA nephropathy, 15 (11%) were diagnosed with benign nephrosclerosis, 12 (9%) were diagnosed with idiopathic membranous nephropathy, nine (6%) were diagnosed with focal segmental glomerulosclerosis, three (2%) were diagnosed with diabetic glomerulosclerosis and 26 (19%) were diagnosed with other conditions. The IF/TA grade exhibited significant correlations with the GS, AA and AO grade (data not shown).

### Relationships between the histopathological parameters and the mean ambulatory BP

The relationships between the mean ambulatory BP and the histopathological parameters were analyzed using a one-way analysis of variance (Table 2). The grade of IF/TA was associated with the mean values of the daytime and nighttime systolic and diastolic BP on ABPM (each  $P < 0.001$ ). The grade of AO was associated with the mean values of the daytime systolic ( $P = 0.003$ ), the diastolic BP ( $P = 0.011$ ) and the nighttime diastolic BP ( $P = 0.034$ ), but not the nighttime systolic BP. In contrast, the grades of GS and AA did not show any statistically significant relationships with the BP values. The significant relationships between the IF/TA grade and the mean values of daytime and nighttime BP remained in the analyses of the patients without apparent renal impairment (eGFR 60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup> or more), those treated without antihypertensive medications, female



**Figure 1** Representative photomicrographs of each histological grade. **(a)** The grade of interstitial fibrosis/tubular atrophy (IF/TA) was evaluated according to semiquantitative methods, as follows: grade 0 = <5%, grade 1 = 5–25% and grade 2 = >25% (Masson-trichrome stain, original magnification  $\times 50$ ). **(b)** The grade of arterial lesions (AA) was defined based on the most severe lesions of intimal thickening by comparing the thickness of the intima (a) to that of the media (b) in the same segment of the vessel. The grade of AA was determined based on the proportion of these values (a/a+b), as follows: grade 0 = absence of intimal thickening, grade 1 = intimal thickening of 50% or less and grade 2 = intimal thickening of >50% (Masson-trichrome stain, original magnification  $\times 200$ ). **(c)** The grade of arteriole lesions (AO) was defined based on the proportion of sites of arteriolar hyalinosis, as follows: grade 0 = <5%, grade 1 = 5–25% and grade 2 = >25% (periodic acid-Schiff stain, original magnification  $\times 400$ ).

patients and nondiabetic patients (data not shown). In contrast, the grade of AO did not exhibit any statistically significant associations with the daytime or nighttime BP values in the analyses of these subgroups (data not shown).

Circadian abnormalities in BP were also analyzed. Of the patients included in this study, 6 (4%) were extreme dippers, 52 (38%) were dippers, 63 (46%) were nondippers and 17 (12%) were reverse dippers. Figure 2 shows the frequency of an NDR of >0.9 for each IF/TA grade. The frequency of an NDR >0.9 increased in association with the IF/TA grade, exhibiting a statistically significant trend ( $P=0.032$ ). This trend remained in the analyses of the patients without apparent renal impairment ( $n=70$ ,  $P=0.007$ ) and those treated without antihypertensive medications ( $n=71$ ,  $P=0.023$ ). In contrast, there were no significant relationships between an NDR >0.9 and the grades of the other histopathological findings, including GS, AA and AO.

#### Relationships between the histopathological parameters and daytime and nighttime hypertension

Forty-nine (36%) patients demonstrated daytime hypertension and 86 (62%) patients displayed nighttime hypertension, as measured on ABPM. Among the 49 patients with daytime hypertension, 48 (98%) patients showed nighttime hypertension.

To determine the effects of the renal function and the severity of IF/TA on the abnormalities in the circadian BP, we examined the prevalence of nighttime hypertension in patients with or without IF/TA grade 2 (>25%) according to the GFR categories (Supplementary Figure). The prevalence of nighttime hypertension in patients with IF/TA grade 2 tended to be higher than that in patients without IF/TA grade 2 in each GFR category. In particular, the prevalence of nighttime hypertension is clearly higher in the patients with IF/TA grade 2, even in the patients with preserved renal function (GFR categories 1 and 2).

Table 3 shows the results of the logistic regression analyses of the factors found to be associated with daytime and nighttime hypertension. In the multivariate analyses, both male gender and an IF/TA grade 2 (>25%) exhibited significant associations with daytime and nighttime hypertension independent of other factors such as the

kidney function, overt proteinuria and the use of antihypertensive medications. We did not find any statistically significant factors associated with an NDR >0.9 in the multivariate analyses (data not shown).

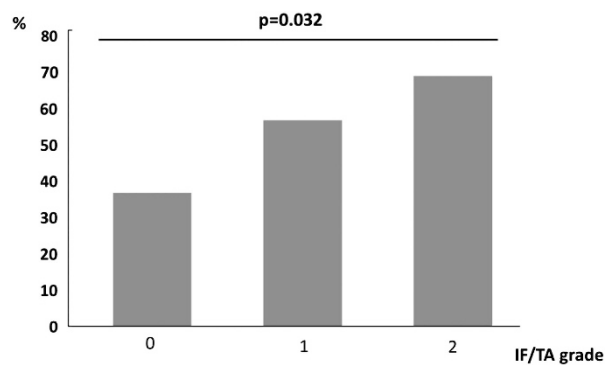
### DISCUSSION

The current results demonstrated that the severity of IF/TA based on the results of renal biopsy specimens exhibits significant associations with increased mean values of the daytime and nighttime BP in CKD patients who have undergone renal biopsies. However, other parameters, including GS, AA and AO, showed only trends or weak relationships with the mean BP values. Moreover, the presence of moderately advanced IF/TA (>25%) showed significant associations with both daytime (>135/85 mm Hg) and nighttime hypertension (>120/70 mm Hg), which is independent of the kidney function, the

**Table 1 Clinical characteristics at the time of the biopsy**

Variable	N = 138
Age (year)	45 ± 15 (15–83)
Male (n (%))	93 (67)
BMI (kg m <sup>-2</sup> )	23.1 ± 3.45 (16.6–37.0)
Current smoker (n (%))	33 (24)
Diabetes mellitus (n (%))	13 (9)
Urinary protein excretion (g per day)	1.24 ± 1.33 (0.03–7.77)
eGFR (ml min <sup>-1</sup> per 1.73 m <sup>2</sup> )	60 ± 28 (5–134)
<i>GFR categories (n (%))</i>	
1	19 (14)
2	51 (37)
3a	28 (20)
3b	18 (13)
4 and 5	22 (16)
<i>Number of patients with hypertensive drugs (n (%))</i>	
0	71 (52)
1	21 (15)
2	25 (18)
3 <	21 (15)
Patients receiving RAS blockades (n (%))	54 (39)
Patients receiving diuretics (n (%))	15 (11)

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin–angiotensin–aldosterone system. Continuous variables are presented as the mean ± s.d.



**Figure 2** Frequency of an NDR >0.9 according to each interstitial fibrosis/tubular atrophy (IF/TA) grade. The frequency of an NDR >0.9 increased in parallel with the grade of IF/TA; this trend was statistically significant ( $P=0.032$ ) by using a Kruskal–Wallis analysis. NDR, night-to-day ratio.

**Table 2 Ambulatory BP and histological parameters: N = 138**

Parameters	Daytime		Nighttime		Daytime		Nighttime	
	SBP	P-value	SBP	P-value	DBP	P-value	DBP	P-value
<b>GS</b>								
0 (N=32)	122 ± 13		112 ± 14		78 ± 8		70 ± 10	
1 (N=57)	123 ± 16		114 ± 18		79 ± 10		73 ± 11	
2 (N=49)	129 ± 16	0.071	121 ± 18	0.082	82 ± 9	0.191	74 ± 10	0.117
<b>IF/TA</b>								
0 (N=21)	120 ± 11		111 ± 12		77 ± 7		68 ± 9	
1 (N=61)	119 ± 10		110 ± 13		77 ± 8		70 ± 10	
2 (N=56)	134 ± 19	<0.001	126 ± 20	<0.001	84 ± 10	<0.001	77 ± 10	<0.001
<b>AA</b>								
0 (N=31)	122 ± 17		113 ± 19		78 ± 11		69 ± 12	
1 (N=68)	125 ± 15		117 ± 16		80 ± 9		74 ± 10	
2 (N=38)	128 ± 16	0.217	119 ± 19	0.375	81 ± 10	0.475	74 ± 10	0.102
<b>AO</b>								
0 (N=38)	120 ± 15		114 ± 17		77 ± 9		70 ± 11	
1 (N=43)	123 ± 15		114 ± 17		79 ± 9		71 ± 10	
2 (N=56)	131 ± 16	0.003	121 ± 18	0.066	83 ± 9	0.011	76 ± 10	0.034

Abbreviations: AA, arterial lesions; AO, arteriole lesions; BP, blood pressure; DBP, diastolic blood pressure; GS, global glomerulosclerosis; IF/TA, interstitial fibrosis/tubular atrophy; SBP, systolic blood pressure.

The analyses were performed using a one-way analysis of variance. Each value of blood pressure is shown by mean ± s.d.



**Table 3** Logistic analyses of daytime and nighttime hypertension: *N* = 138

Variables	Daytime hypertension				Nighttime hypertension			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.03 (1.00–1.05)	0.025	1.01 (0.97–1.04)	0.695	1.05 (1.02–1.08)	<0.001	1.03 (0.99–1.07)	0.142
Gender; male (vs. female)	4.47 (1.81–11.0)	0.001	6.74 (2.22–20.5)	0.001	4.74 (2.21–10.1)	<0.001	6.02 (2.10–17.3)	0.001
BMI	1.04 (0.94–1.15)	0.415	—	—	1.18 (1.05–1.33)	0.006	1.12 (0.98–1.29)	0.091
Anti-hypertensive drugs; yes	2.22 (1.09–4.53)	0.028	0.76 (0.30–1.90)	0.554	3.28 (1.58–6.80)	0.001	0.74 (0.27–1.99)	0.738
eGFR	0.97 (0.96–0.99)	<0.001	0.98 (0.96–1.01)	0.128	0.97 (0.95–0.98)	<0.001	0.99 (0.96–1.02)	0.412
UPE	1.00 (1.00–1.00)	0.020	1.00 (1.00–1.00)	0.445	1.00 (1.00–1.00)	0.006	1.00 (1.00–1.00)	0.299
GS grade 2 (vs. grade 0+1)	2.14 (1.04–4.42)	0.039	0.76 (0.26–2.22)	0.612	2.52 (1.16–5.46)	0.019	0.91 (0.27–3.03)	0.876
IF/TA grade 2 (vs. grade 0+1)	5.10 (2.40–10.8)	<0.001	4.01 (1.34–12.1)	0.013	5.76 (2.50–13.3)	<0.001	5.31 (1.25–22.5)	0.024
AA grade2 (vs. grade 0+1)	2.07 (0.96–4.46)	0.063	—	—	2.06 (0.90–4.71)	0.085	—	—
AO grade2 (vs. grade 0+1)	2.50 (1.22–5.12)	0.012	1.12 (0.45–2.76)	0.809	3.41 (1.57–7.38)	0.002	1.43 (0.55–3.75)	0.467

Abbreviations: AA, artery lesions; AO, arteriole lesions; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GS, global glomerulosclerosis; IF/TA, interstitial fibrosis/tubular atrophy; OR, odds ratio; UPE, urinary protein excretion.

overt proteinuria and the use of antihypertensive medications. Therefore, our results suggest that IF/TA is a more relevant parameter than the other factors of increased mean values of both daytime and nighttime BP in this patient population.

In general, both the severity of IF/TA and frequency of GS increase in association with the progression of renal impairment. In fact, the IF/TA grade exhibited a trend toward an association with the GS grade in our current series (data not shown). Although our results showed a relationship between the grade of IF/TA and BP abnormalities on ABPM, no such relationships were observed between the grade of GS and the ABPM findings. This discrepancy may be explained by the possibility that globally sclerotic glomeruli merge and disappear over long-term periods; thus, the frequency of GS on biopsy specimens may be underestimated.<sup>14</sup> Consistent with this idea are reports that the presence of IF/TA and not GS is the best histopathological parameter of the renal prognosis in patients with various progressive renal diseases.<sup>15–17</sup> Importantly, the relationships between the grade of IF/TA and the prevalence of daytime and nighttime hypertension on ABPM were independent of apparent renal dysfunction in the current study. These results suggest that the association between IF/TA and BP abnormalities does not simply reflect the loss of the entire renal function. Rather, our results suggest the possibility of intrarenal mechanisms controlling systemic BP at the tubulointerstitial level.

Johnson *et al.*<sup>18</sup> proposed the hypothesis that injury to the peritubular capillaries is an important factor in inducing salt-sensitive hypertension. They showed that tubulointerstitial injury induced by transient exposure to cyclosporine is associated with salt-sensitive hypertension in the absence of apparent renal dysfunction.<sup>19</sup> Studies using experimental models of protein overload or cellophane wrapping (pressure injury) of the kidney resulted in salt-sensitive hypertension, further supporting the hypothesis that the tubulointerstitium has an important role in the regulation of the BP in CKD patients.<sup>20,21</sup> Recently, some possible mechanisms underlying the hypertension induced by the tubulointerstitium have been proposed. For example, Oppermann *et al.*<sup>22</sup> found that the angiotensin receptor-associated protein (Atrap), which decreases the effects of angiotensin II receptor type-1 by modulating its trafficking, is expressed in the kidneys, where it localizes in the proximal tubules. Atrap-knockout mice exhibit higher BP and plasma volume values than wild-type mice.<sup>22</sup> Atrap-transgenic mice, which dominantly express Atrap in the

renal tubules, do not display elevated BP values in response to angiotensin II infusion.<sup>23</sup>

It has been reported that the collecting duct produces large amounts of endothelin-1 that binds in an autocrine manner to the endothelin A and B receptors, thereby inhibiting sodium and water reabsorption. The absence of endothelin-1 or its receptors in the collecting duct was shown to be associated with marked salt-sensitive hypertension.<sup>24,25</sup> The results of these experimental studies support the hypothesis that BP is, at least in part, mediated at the level of the renal tubulointerstitial region, which is consistent with our current findings that show a closer relationship between the grade of IF/TA and BP abnormalities than that observed for the other histopathological parameters.

The grade of AO exhibited significant associations with the daytime systolic, nighttime systolic and nighttime diastolic BP values according to the one-way analysis of variance. However, we did not find any significant trends regarding the grade of AO in the multivariate analysis or subgroup analyses of the patients without apparent renal impairment and those treated without antihypertensive drugs. However, the susceptibility to a sampling bias in the arterioarteriolar findings compared with those in the tubulointerstitial findings should be kept in mind. In addition, owing to the limited materials obtained by needle biopsies, we could not determine the intrarenal localization of the specimens and whether the IF/TA was derived from renal vascular lesions (ischemia) or glomerular lesions (glomerulosclerosis). Perera<sup>26</sup> suggested that the occurrence of arteriolar changes in the human kidney is a consequence of hypertensive vascular injury, as they found the severity of vascular lesions to be associated with the duration of hypertension. Castleman and Smithwick<sup>27</sup> evaluated the renal biopsy specimens of patients with essential hypertension obtained during sympathectomy and found that 10–20% of the patients had only mild renal microvascular lesions. Together with these findings, our results suggest that AO may partially reflect renal vascular injury as a result of increased BP.

According to the results of the current multivariate analyses, male gender is significantly associated with both daytime and nighttime hypertension. In addition, further multivariate analyses including diabetes mellitus and current smoking status revealed that male gender was still a significant factor (data not shown). In general, a male gender may be associated with many confounding factors related to hypertension, such as hyperuricemia, smoking and sex hormone

levels.<sup>28–31</sup> It is also known that estradiol is protective against subclinical kidney damage and atherosclerosis.<sup>32,33</sup> Although our study did not address all of the potential factors associated with gender, our results are fully consistent with the findings of previous large-scale studies, demonstrating that male gender is an independent risk factor for the progression of CKD.<sup>34–36</sup>

Our study showed weak but significant relationships between renal histopathological parameters and circadian BP abnormalities. Kimura and group<sup>37,38</sup> proposed the hypothesis that nocturnal hypertension and resultant pressure natriuresis compensate for daytime sodium retention caused by impaired renal sodium excretion in CKD patients. All patients included in our study were Japanese. Approximately 40% of Japanese patients with essential hypertension have been estimated to have salt sensitivity; this rate is expected to be even higher among CKD patients.<sup>39,40</sup> Because ABPM was performed under a sodium-restricted diet during hospitalization in this study, there is a possibility that the trend toward circadian BP abnormalities was modified as a result of sodium restriction. Furthermore, it has been reported that the use of angiotensin type-1 receptor blockers modified the circadian BP measured by ABPM.<sup>41</sup> Therefore, the use of antihypertensive drugs, including angiotensin type-1 receptor blockers, might have influenced the ambulatory BP in the current cohort.

The present study includes several limitations. First, the cause–effect relationships between the histopathological findings and BP abnormalities are unclear as this study was designed as a cross-sectional study. Second, our results may not be applied to all CKD patients because our analyses were limited to patients who underwent renal biopsies. Third, our results may have been modified by the use of bed rest and a sodium-restricted diet during the hospitalization period. Future studies performed at outpatient clinics will help to clarify the relationships between renal histopathological findings and actual ambulatory BP abnormalities in CKD patients.

In conclusion, among four candidate renal histopathological findings, including GS, IF/TA, AA and AO, only IF/TA showed significant associations with various abnormalities on ABPM, including increased mean values of the daytime and nighttime BP, daytime and nighttime hypertension, and circadian BP abnormalities. Although the mechanisms are largely unknown at present, our current results indicate the possibility of tubulointerstitial injury as an origin of BP abnormalities in CKD patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)