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ORIGINAL ARTICLE

Ambulatory blood pressure and tubulointerstitial injury in patients with IgA nephropathy

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Abstract

Background: Few studies have been conducted to assess the ambulatory blood pressure (ABP) in IgA nephropathy (IgAN) patients. This study aimed to determine the relationships between ABP and renal histopathological findings assessed using the Oxford classification (OC) and the Japanese classification (JC), which have recently established histopathological criteria for IgAN.

Methods: This cross-sectional study included biopsy-diagnosed IgAN patients, in whom both a renal biopsy and ABP measurement were performed. The histopathological findings were assessed using the OC and the JC and were analyzed in relation to the ABP.

Results: A total of 111 IgAN patients were included. The score of interstitial fibrosis and tubular atrophy (T score) using the OC was a significantly associated factor with both the daytime and nighttime ABP values. In contrast, the other histopathological scores, including mesangial hypercellularity, endocapillary hypercellularity and segmental glomerulosclerosis, did not show significant associations with the ABP. The histological grade (H-grade) using the JC, which was based on the sum of injured glomeruli, was associated with the daytime ABP, but not with the nighttime ABP. The associations between the T score using the OC (%) and the daytime and nighttime ABP values were independent of age, gender, renal function, proteinuria and the use of antihypertensive medications, whereas the H-grade using the JC (%) did not show significant associations after adjusting for these clinical parameters.

Conclusions: These results suggest that the T score using the OC is the most relevant renal histopathological parameter associated with abnormalities of circadian blood pressure in IgAN patients.

Key words: Oxford classification, IgA nephropathy, ambulatory blood pressure, tubulointerstitial fibrosis, renal biopsy

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Introduction

IgA nephropathy (IgAN) is the most frequently occurring primary glomerulonephritis and is the most common cause of CKD and end-stage kidney disease (ESKD) worldwide [1]. Recent studies have shown that ~35–50% of these patients progress to ESKD within 30 years despite treatments [2, 3].

The Oxford classification (OC) recently established pathological criteria for prediction of the renal prognosis in IgAN patients [4, 5]. The OC identified mesangial proliferation, endocapillary proliferation, segmental glomerulosclerosis and interstitial fibrosis and tubular atrophy (IF/TA) to be independent predictors of renal outcome. Many studies have confirmed the prognostic importance of these histological findings, especially IF/TA, regarding the various degrees of disease severity and race of IgAN patients [6–8]. The Japanese classification (JC) was also proposed to predict the progression to ESKD in IgAN patients [9]. In this classification system, the histological grade (H-grade) identified glomerular lesions, including global and segmental glomerulosclerosis, and extracapillary lesions to be prognostic factors. However, the H-grade does not include IF/TA since the severity of global glomerulosclerosis strongly correlated with the severity of IF/TA. These histological classifications are still being validated for their ability to predict renal prognosis of IgAN patients.

Accumulating evidence has suggested that the measurement of ambulatory blood pressure (ABP) is essential for the diagnosis of hypertension and the evaluation of optimal antihypertensive treatment in CKD patients [10]. ABP monitoring is especially useful for detecting circadian or occasional abnormal blood pressure, such as nocturnal hypertension and white-coat or masked hypertension. Nocturnal hypertension is frequently observed in CKD patients [11]. A subgroup analysis of the CKD-JAC study revealed that the prevalence of masked hypertension was 30.9% in CKD stage G3–5 patients [12]. Of particular importance, these abnormal patterns of blood pressure were shown to be strongly associated with renal and cardiovascular outcomes [13, 14]. In patients with IgAN, hypertensive status has been reported to be one of the important predictors for renal outcome [15, 16]. However, only a few studies have assessed ABP in these patients. In addition, the relationships between ABP and histopathological findings that are able to stratify the risk for renal progression in IgAN patients have not yet been elucidated. By using the OC and the JC, we therefore aimed to determine the histopathological findings that are relevantly associated with ABP abnormalities in IgAN patients.

Materials and methods

Settings and participants

This retrospective cross-sectional study included consecutive patients who underwent percutaneous native renal biopsies and ABP monitoring at the Jikei University Hospital, Tokyo, Japan, during the period from April 2010 to March 2014. The indications for renal biopsy were persistent proteinuria and/or elevated serum creatinine levels. The histopathological diagnosis of IgAN was made by the confirmation of focal or diffuse mesangial proliferation together with predominant deposition of IgA in the mesangial area. The exclusion criteria included (i) patients with Henoch–Schönlein purpura, systemic lupus erythematosus and liver cirrhosis; (ii) patients who have a pathological diagnosis with other renal or systemic diseases and (iii) a biopsy specimen containing less than eight glomeruli. Both the renal biopsies and ABP monitoring were performed during the same hospitalization period. The patients consumed a diet including 6 g/day of sodium chloride during the hospitalization. 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 [no. 26–168 (7673)].

Clinical variables

The clinical information was obtained from the data collected during the hospitalization period. Diabetes mellitus was defined as an HbA1c value ≥6.5% (NGSP) or as patients under medical treatment for diabetes mellitus at the time of a renal biopsy. Hyperuricemia was defined as a uric acid value ≥7 mg/dL or as patients receiving antihyperuricemic medications regardless of gender. The eGFR was calculated by applying a modified three-variable equation for estimating the GFR for Japanese patients [17]: $eGFR = 194 \times age^{-0.287} \times sCr^{-1.094}$ (× 0.739, if female), where sCr is the serum creatinine level. The amount of urinary protein excretion was measured by a 24-h urinary collection.

Measurement of ABP

ABP measurement was planned in all patients who underwent a renal biopsy, regardless of the presence of hypertension when blood pressure is measured during a visit to the doctor's office, to detect any masked hypertension and evaluate the possible risk for renal progression. The ABP monitoring analyses were performed ~4–7 days after admission using a TM-2431C device (A&D, Tokyo, Japan). We defined the ABP parameters as follows: (i) daytime and nighttime ABP were defined as the average of daytime and nighttime mean ABP, respectively, and (ii) the night: day ratio (NDR) was defined as the ratio of the nighttime ABP to daytime ABP [18].

Histopathological analysis

All renal tissue specimens were obtained via percutaneous needle biopsies. The patients' information was blinded at the time of the histopathological evaluation.

The histopathological grading was performed according to the definitions of the OC of IgAN [4, 5]. The definition of the clinical grade (C-grade) and H-grade according to the JC are shown in Supplementary Table S1. The C-grade according to the JC was defined based on the value of the eGFR and the amount of urinary protein excretion. The ratio of prognostic glomeruli (PG) was defined as follows [19]: (number of glomeruli with global and segmental scleroses, or extracapillary lesions/number of total obtained glomeruli × 100 (%)). The H-grade according to the JC was defined based on the PG as follows: H-grade I 0–24.9%, H-grade II 25–49.9%, H-grade III 50–74.9%, and H-grade IV ≥75%.

Statistical analysis

Data are presented as the mean ± SD. For comparisons between two groups, Student's *t*-test or the Mann–Whitney *U*-test was used as appropriate. Differences between three groups were analyzed by a one-way analysis of variance (ANOVA) or the Kruskal–Wallis test as appropriate. The Tukey–Kramer test was used to determine which group caused the difference. Linear regression analyses for both the daytime and nighttime ABP were performed using the forced entry method to determine the effect of histopathological lesions on the ABP. The adjustment variables were those considered to be clinically relevant. Data were analyzed using a commercially available software program (SPSS, Chicago, IL) and P-values <0.05 were considered to be significant in all statistical tests.

Results

Clinicopathological characteristics of patients with IgAN at the time of biopsy

We initially enrolled 128 consecutive patients with biopsy-diagnosed IgAN. Patients were excluded if they had an inadequate renal biopsy specimen of fewer than eight glomeruli ($n = 4$). Among the remaining 124 patients, the ABP value in 111 patients (90%) was measured. The clinicopathological characteristics of the 13 patients who did not receive ABP monitoring were comparable to the 111 patients included in this study (data not shown). The clinicopathological characteristics of the IgAN patients at the time of biopsy are summarized in Table 1. Approximately half of these patients were not taking antihypertensive medications. Sixty-four (58%) of these patients were those with preserved renal functions (eGFR ≥60 mL/min/1.73 m^2). Sixteen (14%) and 45 (41%) of these patients were hypertensive according to the office blood pressure (≥140/90 mmHg) and ABP (≥130/80 mmHg), respectively [20]. Thirty-two (29%) and three (3%) patients showed masked (normotensive by office blood pressure and hypertensive by ABP) and white-coat (hypertensive by office blood pressure and normotensive by ABP) hypertension, respectively. The distribution of the histopathological findings was comparable to those of previously reported large IgAN patient cohorts [5, 6].

Table 1. Clinicopathological characteristics of patients with IgAN at the time of biopsy

Clinical findings	
Age, years	40 ± 13 (15–70)
Male, *n* (%)	73 (66)
BMI, kg/m^2	22.6 ± 3.5
Current smoker, *n* (%)	16 (14)
No. of antihypertensive medications, *n* (%)	0.8 ± 1.0
0	61 (55)
1	20 (18)
2	19 (17)
3	11 (10)
ACE-I/ARB, *n* (%)	37 (33)
Diuretics, *n* (%)	2 (2)
Corticosteroids, *n* (%)	5 (5)
Diabetes mellitus, *n* (%)	3 (3)
Hyperuricemia, *n* (%)	54 (49)
Urinary protein excretion, g/day	1.2 ± 1.8 (0.1–7.7)
eGFR, mL/min/1.73 m^2	64 ± 26 (11–121)
GFR stage, *n* (%)	
G1	17 (15)
G2	47 (42)
G3a	19 (17)
G3b	13 (12)
G4, 5	15 (14)
Office blood pressure, mmHg	122/73
24-h ABP, mmHg	119/77
Daytime ABP, mmHg	121/79
Nighttime ABP, mmHg	111/70
NDR of ABP	0.90
Histopathological findings, *n* (%)	
M1	35 (32)
E1	30 (27)
S1	83 (75)
T1/T2	20/17 (18/15)
Global glomerulosclerosis, %	22 ± 21
Segmental glomerulosclerosis, %	7 ± 8
Crescentic lesion present, *n* (%)	66 (59)
Cellular/fibrocellular/fibrous, *n* (%)	19(17)/51(46)/38(34)
PG, %	35 ± 23
H-grade I, *n* (%)	48 (43)
H-grade II, *n* (%)	32 (29)
H-grade III + IV, *n* (%)	31 (28)

Values are given as the mean ± SD (range) unless otherwise indicated.
BMI, body mass index; ACE-I, angiotensinogen-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; PG, the ratio of prognostic glomeruli to total obtained glomeruli according to the JC.

Comparison of the ABP according to the histopathological findings using the Oxford classification

The relationships between the ABP and the histopathological findings using the OC in all patients ($n = 111$) are shown in Table 2. There were no significant differences in the daytime and nighttime ABP values between M0 versus M1, E0 versus E1 and S0 versus S1. In contrast, the daytime and nighttime ABP values were significantly different among the three groups according to the T score (one-way ANOVA). There was a significant difference between T0 versus T2 according to a *post hoc* analysis in both the daytime and nighttime ABP. Moreover, patients with more severe T scores tended to demonstrate a higher ABP. The subgroup analyses of the patients not taking antihypertensive medications ($n = 61$), patients without advanced renal function decline (eGFR >30 mL/min/1.73 m^2; $n = 96$), patients with renal function decline (eGFR <60 mL/min/1.73 m^2; $n = 45$) and patients with overt proteinuria (urinary protein excretion >0.5 g/day; $n = 77$) are given in Supplementary Tables S2–S5. As well as in the analysis in all patients, patients with more severe T scores tended to demonstrate a higher ABP in these subgroup analyses, although the nighttime ABP value between T0 versus T1 and T2 in the patients not taking antihypertensive medications and the ABP value among T scores in the patients with renal function decline and those with overt proteinuria did not reach statistical significance.

There were weak but significant relationships between the arteriole lesion scores and both the daytime and nighttime ABP values in the analyses in all patients, but not in the subgroup analyses of the patients not taking antihypertensive medications. No significant histopathological parameter was found to be associated with the NDR.

Comparison of ABP according to grading by the Japanese classification

The relationships between ABP and the C- and H-grades using the JC in the analyses of all patients ($n = 111$) are given in Table 3. Overall, the daytime ABP was significantly different among the patients categorized according to the H-grade using the JC, whereas the nighttime ABP was not. There were no significant relationships in either the daytime or nighttime ABP in the subgroup analysis of the patients not taking antihypertensive medications (Supplementary Table S2). In contrast, the C-grade using the JC was strongly associated with both the daytime and nighttime ABP values in the analyses of all patients and the patients not taking antihypertensive medications.

Multiple linear regression analyses of the daytime and nighttime ABP values

To compare the influences of the severity of IF/TA according to the OC and the PG according to the JC on blood pressure, we performed multiple linear regression analyses for the daytime

Table 2. Comparison of the mean value and NDR of ABP according to the Oxford classification ($n = 111$)

	M0 ($n = 76$)	M1 ($n = 35$)		P-value
Daytime mean ABP	93 ± 10	92 ± 12		0.727
Nighttime mean ABP	84 ± 12	83 ± 13		0.648
NDR	0.90 ± 0.08	0.90 ± 0.06		0.680
	E0 ($n = 81$)	E1 ($n = 30$)		
Daytime mean ABP	93 ± 11	93 ± 10		0.861
Nighttime mean ABP	84 ± 13	84 ± 11		0.841
NDR	0.90 ± 0.07	0.90 ± 0.07		0.840
	S0 ($n = 28$)	S1 ($n = 83$)		
Daytime mean ABP	94 ± 11	92 ± 10		0.597
Nighttime mean ABP	85 ± 15	83 ± 12		0.636
NDR	0.90 ± 0.07	0.90 ± 0.07		0.952
	T0 ($n = 74$)	T1 ($n = 20$)	T2 ($n = 17$)	
Daytime mean ABP	91 ± 9	95 ± 10	98 ± 15[a]	0.012
Nighttime mean ABP	82 ± 11	85 ± 12	92 ± 16[a]	0.010
NDR	0.90 ± 0.07	0.89 ± 0.08	0.93 ± 0.07	0.210
	AA0 ($n = 26$)	AA1 ($n = 56$)	AA2 ($n = 29$)	
Daytime mean ABP	90 ± 10	93 ± 9	95 ± 13	0.240
Nighttime mean ABP	79 ± 11	84 ± 11	87 ± 16	0.052
NDR	0.88 ± 0.06	0.91 ± 0.07	0.92 ± 0.08	0.111
	AO0 ($n = 25$)	AO1 ($n = 43$)	AO2 ($n = 42$)	
Daytime mean ABP	89 ± 8	93 ± 12	95 ± 10	0.048
Nighttime mean ABP	81 ± 8	82 ± 14	88 ± 12	0.049
NDR	0.91 ± 0.04	0.89 ± 0.07	0.92 ± 0.08	0.129

Values are shown as the mean ± SD.
AA, arterial lesions; AO, arteriole lesions. [a]Significant difference versus T0 using the Tukey–Kramer test.

Table 3. Comparison of the mean value and NDR of ABP according to the Japanese classification ($n = 111$)

	C-grade I ($n = 34$)	C-grade II ($n = 39$)	C-grade III ($n = 38$)	P-value
Daytime mean ABP	88 ± 7	93 ± 9	96 ± 12[a]	0.002
Nighttime mean ABP	79 ± 10	83 ± 11	88 ± 14[a]	0.004
NDR	0.89 ± 0.08	0.90 ± 0.06	0.91 ± 0.08	0.470
	H-grade I ($n = 48$)	H-grade II ($n = 32$)	H-grade III/IV ($n = 31$)	
Daytime mean ABP	90 ± 9	92 ± 9	97 ± 13[a]	0.021
Nighttime mean ABP	81 ± 11	84 ± 10	88 ± 15	0.087
NDR	0.90 ± 0.07	0.91 ± 0.07	0.90 ± 0.08	0.936

Values are shown as the mean ± SD.
[a]Significant difference versus Grade I using the Tukey–Kramer test.

and nighttime ABP values (Table 4). The severity of IF/TA (%) and the PG (%) were significantly associated with both the daytime and nighttime ABP values according to the univariate analyses (Model 1). The severity of IF/TA was a significant factor associated with both the daytime and nighttime ABP, independent of age, gender, eGFR, proteinuria and the use of antihypertensive medications (Models 2–5). In contrast, the PG was not a significant parameter associated with the daytime or nighttime ABP after adjusting for these clinical variables (Models 3–5).

Discussion

This cross-sectional study showed that the T score using the OC was closely correlated with both the daytime and nighttime ABP, whereas the other histopathological scores were not in IgAN patients. The H-grade using the JC, which is based on the sum of the glomerular lesions, was associated with daytime ABP, but not nighttime ABP (Tables 2 and 3). Almost similar trends were observed in the subgroup analyses of the patients with and without severe disease involvement, including renal function decline or overt proteinuria (Supplementary Tables S3–S5). In the multiple linear regression analyses, the T score according to the OC was significantly associated with both the daytime and nighttime ABP, independent of important clinical variables, including age, gender, eGFR, proteinuria and the use of antihypertensive medications. In contrast, the PG (%) using the JC was not significantly associated with the ABP after an adjustment for these variables (Table 4).

It is well accepted that IF/TA is a feature of the final common pathway in advanced renal disease and the most precise

Table 4. Multiple linear regression analyses for the daytime and nighttime ABP values

	IF/TA		PG	
	Standardized β	P-value	Standardized β	P-value
Daytime ABP				
Model 1	0.338	<0.001	0.275	0.004
Model 2	0.312	0.001	0.252	0.009
Model 3	0.284	0.047	0.139	0.300
Model 4	0.321	0.022	0.177	0.173
Model 5	0.329	0.024	0.176	0.180
Nighttime ABP				
Model 1	0.318	0.001	0.242	0.011
Model 2	0.263	0.006	0.181	0.064
Model 3	0.242	0.092	0.072	0.533
Model 4	0.294	0.040	0.110	0.408
Model 5	0.313	0.035	0.110	0.411

Model 1 was unadjusted; Model 2 was adjusted for age and gender; Model 3 was adjusted for the eGFR and amount of urinary protein excretion; Model 4 was adjusted for covariates in Models 2 and 3; Model 5 was adjusted for covariates in Model 4 plus the use of antihypertensive medications (versus no medication). PG, the ratio of prognostic glomeruli to total obtained glomeruli according to the JC.

predictor for the renal prognosis in several types of progressive renal diseases, including IgAN [21–23]. Importantly, our current study showed that the severity of IF/TA was significantly associated with ABP independent of the renal disease involvement, suggesting that the association between ABP and IF/TA is not simply the result of renal impairment, and these correlations might occur in an earlier stage of renal disease. In support of this idea, significant relationships between the salt-sensitivity index and the severity of IF/TA in normotensive IgAN patients with preserved renal function were reported [24]. In addition, an epidemiological study from Japan showed a significant positive correlation between the casual blood pressure and the urinary beta-2 microglobulin:creatinine ratio (which reflects the severity of tubulointerstitial damage) in the general population without an apparent renal function decline [25].

Consistent with our current results, previous studies have suggested that tubulointerstitial mechanisms directly mediate abnormalities in blood pressure. Johnson *et al.* [26] hypothesized that renal interstitial inflammatory and tubular changes play a critical part in inducing salt-sensitive hypertension. They demonstrated that exogenous IF/TA using protein overload or cellophane wrapping (pressure injury) of the kidney in experimental rat models could cause salt-sensitive hypertension [27, 28]. More recently, several possible mechanisms underlying hypertension induced by the tubulointerstitium have been proposed, such as angiotensin II and its receptor axis [29, 30], including angiotensin II type1 receptor-associated protein [31, 32], dopamine [33, 34] and endothelin-1 [35]. The results of these experimental studies support the hypothesis that blood pressure could be, at least in part, regulated by the renal tubulointerstitium.

It is difficult to compare directly the superiority of the OC with that of the JC. Since the OC applies a split system, it is useful to simply describe the predictive value of each histopathological grade in IgAN. Our current results may therefore add valuable meaning to the T score using the OC regarding its relationship with circadian blood pressure abnormalities in IgAN patients. In contrast, the JC uses a lumped system consisting of the C-grade, based on the eGFR value and proteinuria, and the H-grade, based on the PG. In this study, the C-grade using the JC was well correlated with both the daytime and nighttime ABP. These results suggested that the C-grade may compensate for the blood pressure effect on the renal prognosis of IgAN. Indeed, Okonogi *et al.* [36] showed that risk stratification using only eGFR values and the amount of urinary protein excretion could predict the long-term renal outcome in IgAN patients. However, whether ABP monitoring is superior to the office blood pressure measurement and stratification according to eGFR and proteinuria for predicting renal outcome in IgAN patients must be confirmed.

The arteriole (AO) grade exhibited significant associations with the daytime and nighttime ABP in the patients overall, but not in patients not taking antihypertensive medications. However, these findings must be carefully interpreted due to potential sampling bias. In addition, due to the limited specimens obtained by the needle biopsies, we could not determine the intrarenal localization of the specimens. The results of previous autopsy and biopsy studies in patients with essential hypertension suggested that the AO lesions might reflect the consequence of increased blood pressure [37, 38].

There are several limitations associated with the present study. First, the cause–effect relationships between the renal histopathological findings and the ABP values were undetermined since our study was designed as a cross-sectional study. Secondly, the ABP values might have been modified by decreased physical activity and diet with 6 g/day of sodium chloride during the hospitalization period. Future studies performed at outpatient clinics will help to clarify this issue.

In conclusion, our results suggest that the T score according to the OC is the most relevant renal histopathological parameter associated with ABP values in IgAN patients. Although the detailed mechanisms are largely undetermined at present, our results indicate the novel advantage of the T score using the OC for predicting functional abnormalities of circadian blood pressure regulation in IgAN patients.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement

None declared.

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