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Prevalence and clinical characteristics of primary aldosteronism in Japanese patients with type 2 diabetes mellitus and hypertension

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Abstract. The prevalence of primary aldosteronism (PA) is around 3–15% in patients with hypertension. Hypertension is a frequent complication of type 2 diabetes mellitus (DM) because of the close etiological relationship between these two diseases. However, the possibility of PA in patients with DM and hypertension is often overlooked and the prevalence of PA in patients with DM and hypertension in Japan is unknown. We enrolled 124 hospitalized patients with both DM and hypertension. PA was diagnosed according to the modified criteria for Japanese patients. We examined the prevalence of PA and compared clinical characteristics between patients with and without PA. In another analysis of 43 patients with a confirmed diagnosis of PA, we compared the characteristics of patients with and without DM. Overall, 14/124 patients with DM and hypertension (11.3%) were diagnosed with PA. Multivariate logistic regression showed that the duration of DM was significantly shorter in the PA group. Fisher's direct probability test revealed that history of hypertension before the diagnosis of DM was a significant factor in patients with PA. Treatment with an angiotensin II receptor blocker (ARB) did not affect the diagnosis of PA in these patients. Among 43 patients with PA, those with DM were significantly older and the delay to the diagnosis of PA was significantly longer compared with patients without DM. In conclusion, almost 10% of patients with DM and hypertension actually have PA. More extensive screening for PA is recommended in patients with DM and hypertension, regardless of the use of ARBs.

Key words: Primary aldosteronism, Type 2 diabetes mellitus, Hypertension

PRIMARY ALDOSTERONISM (PA) is characterized by autonomic oversecretion of aldosterone from the adrenal gland, resulting in increased renal sodium uptake and potassium excretion. Patients with PA often show secondary hypertension and sometimes hypokalemia [1]. PA is usually caused by an adrenal adenoma, although other causes exist, including bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), for example. The prevalence of PA in hypertensive patients is estimated to be around 3.3–15.0% in Japan and in other countries [2-5]. Therefore, it seems that clinicians are increasingly becoming more aware of PA as a cause of hypertension. One reason for this increasing awareness may be widespread dissemination

of the Japanese guidelines for PA published in 2011[1].

PA is also very commonly associated with impaired glucose tolerance, being present in almost 50% of individuals with IGT [6-8]. Although one of the underlying mechanisms, suppression of insulin secretion by low serum potassium is well recognized, aldosterone was also reported to directly inhibit insulin secretion from cultured pancreatic β cells [9]. In addition, aldosterone induces IGT by stimulating the production of molecules that cause insulin resistance, including free fatty acids (FFA) and tumor necrosis factor, from adipocytes [10].

It was reported that 62% of patients with type 2 diabetes mellitus (DM) also have hypertension [11]. The coexistence of hypertension and DM accelerates the course of microvascular and macrovascular disease [12]. In DM, hyperinsulinemia caused by insulin resistance increases renal sodium uptake [13] and sympathetic nerve activity [14], which induce hypertension. The progression of diabetic nephropathy and atherosclerosis is also thought to be associated with the high

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prevalence of hypertension in patients with DM [12]. However, the prevalence of PA in patients with both DM and hypertension in Japan is unknown. In most patients with both DM and hypertension, the possibility of having PA is often overlooked, probably because DM and hypertension are well known to coexist. The frequent use of antihypertensive drugs, particularly angiotensin II receptor blockers (ARBs), in patients with DM and hypertension may also contribute to delays in performing screening tests for PA.

Three studies have reported the coexistence of PA and DM as a result of screening of hypertensive patients. In one study, the prevalence of PA was 14% in diabetic subjects ($n = 100$) with poorly controlled hypertension taking more than three antihypertensive drugs [15]. In that study, most subjects were African-Americans (93%). In another study of 100 consecutive Asian patients with type 2 DM with difficult to control or resistant hypertension, 13% of patients were diagnosed as PA [16]. More recently, in a study of 232 Chinese hypertensive patients, PA was found in 14–23%, 2.3–23.3%, and 9.1% of patients with DM, impaired glucose tolerance, and impaired fasting glucose, respectively [17]. In these studies, plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio (ARR) ≥ 200 [17], ≥ 300 [15], or ≥ 550 [16] and lack of PAC suppression following administration of 2 L of 0.9% saline over 4 h were used to screen for and confirm the diagnosis of PA. However, no such studies have been conducted in Japan. Furthermore, the clinical characteristics, including the sequence of the diagnosis of hypertension and DM, or the impact of ARBs on ARR in screening were not fully examined in the previous studies [15–17].

In this study, to determine the prevalence of PA in Japanese patients with DM and hypertension, we performed a retrospective analysis of 124 patients whose ARR was assessed. We found that 11.3% of these patients had PA, which was close to that observed among general hypertensive patients. In this report, we compared the clinical characteristics of patients with DM and hypertension with or without PA.

Methods

Subjects and diagnosis of PA

This research project was approved by the institutional board review on clinical research. Of 585 cases manifesting both DM and hypertension who were hospitalized in our department between April 1, 2009,

and August 31, 2012, the PAC/PRA ratio (ARR) was assessed in 124 patients, who were included in this study because of their stable general condition. The remaining 461 patients had clinical disorders (*e.g.*, diabetic ketosis, hyperosmolar non-ketotic syndrome, severe diabetic complications, severe infections, the need for rapid blood glucose control before operation, fragility, and a bedridden state) that meant they were unsuitable for inclusion in this study. Of the 124 patients, 79 were men (63.7%) and their clinical characteristics are shown in Table 1. Hypertension was defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg according to the guidelines of the Japan Society of Hypertension 2009 [18]. Type 2 DM was defined according to the guidelines of the Japan Diabetes Society 2012 [19]. Insulin was used in 40/124 patients with DM. Oral hypoglycemic agents were also used, including sulfonylureas (SUs) in 27 patients, biguanides in 24 patients, α -glucosidase inhibitors (α -GIs) in 10 patients, thiazolidinediones (pioglitazone) in 6 patients, glinides in 4 patients, and dipeptidyl peptidase-4 inhibitors in 28 patients. Because it is unethical and unsafe to discontinue prescribed therapies, ARR was measured while the patients were using their antihypertensive and antidiabetic drugs. The antihypertensive drugs used at the measurement of ARR are shown in Table 2. If ARR was ≥ 200 , the antihypertensive medications, including ARBs, angiotensin converting enzyme inhibitors (ACEI), β -blockers, and diuretics, were stopped and only calcium channel blockers (CCB), mostly nifedipine (10–20 mg/day) were administered for 3–5 days. The following tests were then performed in patients with an ARR ≥ 200 . PA was diagnosed in patients with ARR ≥ 200 and who had positive outcomes for at least two of the following three tests: upright furosemide-loading test, captopril challenge test, and rapid adrenocorticotrophic hormone (ACTH) loading test. In the upright furosemide-loading test and the captopril-challenge test, positive outcomes were defined as PRA < 2.0 ng/mL-h or ARR ≥ 200 , respectively, according to Japan Endocrine Society guidelines [1]. In addition to these guidelines, the usefulness of the ACTH loading test has been emphasized and is commonly performed in Japan [20, 21]. In the rapid ACTH loading test, serum PAC (pg/mL) /cortisol (μ g/dL) ≥ 8.5 were considered positive outcomes for PA [20].

Adrenal venous sampling (AVS) was performed by expert radiologists according to our previously reported method [22]. Briefly, synthetic ACTH (1–24 ACTH)

Table 1 Clinical characteristics of 124 patients with DM and hypertension with or without PA

	Total		PA		Non PA		<i>t</i> -test, Fisher
	n	Mean $\pm$ S.D.	n	Mean $\pm$ S.D.	n	Mean $\pm$ S.D.	<i>P</i> value
Age	124	63.01 $\pm$ 12.08	14	65.57 $\pm$ 8.01	110	62.68 $\pm$ 12.49	0.402
Sex (male/female)	124	79 / 45	14	8 / 6	110	71 / 39	0.572
Duration of DM (yr)	120	12.84 $\pm$ 11.3	14	5.21 $\pm$ 6.51	106	13.73 $\pm$ 11.43	0.007
Duration of HT (yr)	105	11.55 $\pm$ 11.48	14	13.15 $\pm$ 11.60	91	11.14 $\pm$ 11.52	0.582
BMI (kg/m ²)	122	25.68 $\pm$ 4.96	14	23.95 $\pm$ 2.37	108	25.90 $\pm$ 5.16	0.21
Systolic BP (mmHg)	124	142.4 $\pm$ 22.45	14	142.64 $\pm$ 22.13	110	142.35 $\pm$ 22.59	0.964
Diastolic BP (mmHg)	124	79.84 $\pm$ 13.59	14	79.64 $\pm$ 14.94	110	79.86 $\pm$ 13.48	0.549
Number of antihypertensive drug	124	1.34 $\pm$ 1.24	14	1.75 $\pm$ 1.49	110	1.27 $\pm$ 1.21	0.214
PAC (pg/mL)	124	87.11 $\pm$ 66.94	14	167.9 $\pm$ 84.06	110	76.83 $\pm$ 57.17	0.0001
PRA (ng/mL·hr)	124	2.16 $\pm$ 3.80	14	0.26 $\pm$ 0.18	110	2.40 $\pm$ 3.97	0.001
ARR	124	200.50 $\pm$ 432.47	14	936.49 $\pm$ 962.48	110	100.47 $\pm$ 100.88	0.0062
Na (mEq/L)	124	139.68 $\pm$ 3.52	14	140.9 $\pm$ 4.14	110	139.52 $\pm$ 3.43	0.350
K (mEq/L)	124	4.13 $\pm$ 0.48	14	3.82 $\pm$ 0.49	110	4.17 $\pm$ 0.47	0.010
Cr (mg/dL)	124	1.22 $\pm$ 1.09	14	0.88 $\pm$ 0.32	110	1.27 $\pm$ 1.14	0.215
eGFR (mL/min/1.73m ²)	124	62.01 $\pm$ 26.70	14	65.26 $\pm$ 17.47	110	61.60 $\pm$ 27.69	0.631
Microalbuminuria (mg/g/Cr)	54	63.08 $\pm$ 108.25	9	42.60 $\pm$ 92.39	45	67.17 $\pm$ 111.63	0.539
FBS (mg/dL)	124	159.20 $\pm$ 58.48	14	115.29 $\pm$ 21.21	110	164.79 $\pm$ 59.38	0.0001
HbA1c (NGSP) (%)	124	8.61 $\pm$ 1.92	14	7.26 $\pm$ 1.43	110	8.79 $\pm$ 1.91	0.005
Urine C peptide (μ g/day)	114	74.99 $\pm$ 57.36	10	76.49 $\pm$ 32.43	104	74.84 $\pm$ 59.31	0.932

P values were determined using Student's independent-samples *t*-test and were considered to be statistically significant at *P* < 0.05. DM, diabetes mellitus; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone/renin ratio

Table 2 Types of antihypertensive drugs at the measurement of ARR in patients with PA with or without DM

	Total (%)	PA (%)	Non PA (%)
ARB	58 (46.8)	5 (35.7)	53 (48.1)
CCB	58 (46.8)	11 (78.6)	47 (42.7)
Diuretic drug	11 (8.9)	1 (7.1)	10 (9.1)
ACE-I	2 (1.6)	1 (7.1)	1 (0.9)
α -blocker	10 (7.8)	4 (28.6)	6 (5.5)
β -blocker	7 (5.6)	3 (21.4)	4 (3.6)
Selective aldosteron blocker	1 (0.8)	1 (0.9)	0 (0)
Direct renin blocker	2 (1.6)	0 (0)	2 (1.8)

ARR, aldosterone/renin ratio; DM, diabetes mellitus; PA, primary aldosteronism; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor

was intravenously administered at 50 μ g/h from 60 min before AVS until the end of AVS. Blood samples were taken from the proximal inferior vena cava (IVC), left adrenal vein, right adrenal vein, and distal IVC. Adrenal vein cannulation was considered successful if the adrenal vein cortisol level was ≥ 200 μ g/dL or if the adrenal vein/IVC cortisol ratio was ≥ 5 . The patient was diagnosed with aldosterone hypersecretion (*i.e.*, PA) if the PAC was $\geq 14,000$ pg/mL in either or both of the adrenal veins. Lateralization was considered if the aldosterone to cortisol ratio (A/C) from one adrenal gland was ≥ 3 times the ratio of the other adrenal gland (lateralization ratio [LR]) and the A/C in the contralateral adrenal vein was lower than the A/C in the IVC (contralateral ratio

[CR]), as previously described [23].

Although AVS was only performed in 22 patients between April 1, 2009 and August 31, 2012, we calculated sensitivity, specificity, and accuracy of our diagnostic criteria of PA by discriminate analysis based on positive outcomes for at least two of the following three tests: upright furosemide-loading test, captopril challenge test, and rapid ACTH loading test. The sensitivity, specificity, and accuracy were 95.0%, 100% and 95.2%, respectively, for satisfying the criteria of both the upright furosemide-loading test and the captopril-challenge test; were 95.2%, 100% and 95.5 %, respectively, for satisfying the criteria of both the upright furosemide-loading test and the rapid ACTH test; and

were 90.5%, 100%, and 90.9%, respectively, for satisfying the criteria of both the captopril-challenge test and the rapid ACTH test. The sensitivity, specificity, and accuracy for satisfying the criteria of all three tests were 90.5 %, 100%, and 90.9%, respectively.

Next, we compared the clinical characteristics of patients with and without PA, focusing on their age, sex, body mass index (BMI), duration of hypertension, duration of DM, type of antihypertensive drugs, PRA, PAC, serum creatinine, serum Na, serum K, fasting blood sugar (FBS), HbA1c (National Glycohemoglobin Standardization Program [NGSP] units), and 24-h urine C-peptide immunoreactivity (CPR). FBS was measured using an automatic glucose monitor (GA-1170; ARKRAY, Inc., Kyoto, Japan) based on the amperometric method. The effects of using different first-line antihypertensive drugs in patients with DM, including ARBs, ACEIs, and CCBs [18, 24, 25] on ARR and the diagnosis of PA were also investigated.

In 43 patients with a confirmed diagnosis of PA who were hospitalized at our department between April 1, 2009, and August 31, 2012, we compared the clinical characteristics of those with and without DM. The sequence of the diagnosis of DM and hypertension was obtained from the clinical records based on the patient's medical history.

Statistical analysis

All data are expressed as means $\pm$ standard deviation. Univariate analyses were performed using Student's independent-samples *t*-test. For multivariate analyses, we used logistic regression or Fisher's test, as appropriate. Values of $P < 0.05$ were considered statistically significant.

Results

Prevalence of PA in patients with DM and hypertension

In the observation period, 585 patients with both DM and hypertension were hospitalized at our department. ARR was measured in 124 of these patients, and their characteristics are summarized in Table 1. The mean age was 63.01 ± 12.08 years old. The mean durations of DM and hypertension were 12.84 ± 11.3 years and 11.55 ± 11.48 years, respectively. The mean systolic and diastolic blood pressures (BP) were 142.4 ± 22.45 mmHg and 79.84 ± 13.59 mmHg, respectively. Most of the 124 patients had poor glycemic control because the mean HbA1c (NGSP) level was $8.61 \pm 1.92\%$.

ARR was ≥ 200 in 23/124 patients. Of these, six had low PRA and low PAC (<70 pg/mL) as a result of severe diabetic neuropathy, giving the appearance of ARR ≥ 200 , and were excluded from further analyses. The other 17 patients underwent loading or suppression tests to confirm the diagnosis of PA and 14 patients were positive on more than two tests. Of these 14 patients, nine patients were positive on all three tests and three patients were positive on two tests. The other two patients had ARR values of 1390 and 917, respectively, and both satisfied the criteria of the upright furosemide-loading test and the captopril challenge test. However, neither of these patients wished to undergo the ACTH loading test. Therefore, these 14 patients were ultimately diagnosed with PA, corresponding to 11.3% of the subjects with DM and hypertension.

Clinical characteristics of patients with DM and hypertension with PA or without PA

Next, we compared the characteristics of patients with DM and hypertension together with PA ($N = 14$) or without PA ($N = 110$) (Table 1). There were no significant differences in terms of age, sex, BP, BMI, or the number of antihypertensive drugs. However, duration of DM was significantly shorter in patients with PA (5.21 ± 6.51 years) than in those without PA (13.73 ± 11.43 years) (Table 1). Multivariate logistic regression analysis showed that a shorter duration of DM, but no other variable, was significantly associated with the occurrence of PA (Table 3). On the other hand, the duration of hypertension was not significantly different between the two groups. The history of DM and hypertension could be assessed in 14 patients with PA and in 91 patients without PA. Hypertension was diagnosed before DM in 8/14 patients with PA, and in 17/91 patients without PA. DM was diagnosed before hypertension in 3/14 patients with PA, and in 43/91 patients without PA. Hypertension and DM were diagnosed at the same time in 3/14 patients with PA and in 31/91 patients without PA. Fisher's direct probability test revealed that the difference in the sequence of diagnosis of HT and DM significantly contributed to the diagnosis of PA as patients with PA were significantly more likely than patients without PA to be diagnosed with hypertension before DM ($P = 0.013$; Fig. 1). The mean serum K level was significantly lower in patients with PA than in those without PA (3.82 vs. 4.17 mEq/L). However, the serum K level was within the normal range (>3.5 mEq/L) in 13/14 patients with PA (92.8%); the other patient had a very low serum K level

Table 3 Multivariate logistic regression analysis of factors associated with PA in patients with DM and hypertension (n=124)

	Regression coefficient	S.E	P value	Contribution	Odds ratio (95% C.I)
Sex	0.415	0.776	0.5926	0	1.52 (0.33-6.93)
Age	0.008	0.038	0.8327	0	1.01 (0.93-1.09)
BMI	-0.194	0.109	0.768	-0.13	0.82 (0.66-1.02)
Duration of DM	-0.095	0.047	0.0463	-0.18	0.91 (0.82-0.99)
Duration of HT	0.045	0.033	0.1791	0	1.05 (0.97-1.12)
Systolic BP	0.007	0.022	0.7528	0	1.01 (0.96-1.05)
Diastolic BP	-0.02	0.041	0.5421	0	0.98 (0.89-1.06)

DM, diabetes mellitus; PA, primary aldosteronism; HT, hypertension; BP, blood pressure

In the case of sex, male and female was defined as 1 and 2, respectively.

Fig. 1 Comparison of the sequence of diagnosis of hypertension (HT) and diabetes mellitus (DM) in patients with or without primary aldosteronism. black column, patients with PA; dark column, patients without PA. Fisher's direct probability test revealed that the sequence of diagnosis of HT and DM significantly contributed to the diagnosis of PA ($P = 0.013$).

(2.3 mEq/L). Regarding other factors, FBS and HbA1c were significantly lower in patients with PA than in those without PA, but 24-h urinary CPR was not significantly different between the two groups (Table 1).

Effects of antihypertensive drugs on ARR

The effects of antihypertensive drugs on PRA, PAC, ARR, and the diagnosis of PA were investigated. The types of antihypertensive drugs used at the measurement of ARR in patients with and without PA are listed in Table 2. Because most of the patients were prescribed with an ARB and/or CCB, we focused on these two classes of drugs. The values of PAR, PAC, and ARR differed, although not significantly, between those treated with or without an ARB in all 124 patients, and between those with or without PA (Table 4). Fisher's analysis confirmed that treatment with an ARB or CCB did not affect ARR. The P values in these analyses for the use of an ARB or CCB were 0.941 and 0.17, respectively.

Further examination and the treatment of hypertension in PA patients

Of 14 diabetic patients with PA, 12 underwent AVS. Based on the results of this test, four patients were

diagnosed with bilateral aldosterone-producing disorders and eight patients were diagnosed with unilateral aldosterone-producing disorders. Among eight patients with unilateral adrenal disorders, abdominal computed tomography found no evidence of an adrenal tumor in two patients, contralateral adrenal tumors in two patients, and an adrenal tumor located in the affected adrenal gland in four patients. Only one patient had undergone unilateral adrenalectomy, and an adrenal adenoma was pathologically confirmed in this patient. Although her hypertension improved after adrenalectomy, she needed to continue her antihypertensive drugs. Hypertension was well controlled in the other 13 patients ($<140/90$ mmHg), mostly with CCBs, eplerenone, or both.

Clinical characteristics of patients with PA with DM or without DM

Among the 43 patients with a confirmed diagnosis of PA, 15 had DM (34.9%) and 28 did not. The clinical characteristics of both groups are summarized in Table 5. The patients with DM were significantly older (66.45 ± 8.43 vs. 55.07 ± 10.53 years) and their diagnosis of DM was considerably delayed (17.44 ± 11.28

Table 4 Effect of ARBs on PRA, PAC, and ARR in patients with DM and hypertension

		ARB (+)	ARB (-)	P value
	n	58	66	
Total	PRA ($\pm$ SD)	2.77 ($\pm$ 4.57)	1.62 ($\pm$ 2.89)	0.095
	PAC ($\pm$ SD)	76.90 ($\pm$ 65.2)	96.08 ($\pm$ 67.7)	0.118
	ARR ($\pm$ SD)	128.9 ($\pm$ 190.7)	246.4 ($\pm$ 545.9)	0.122
	n	5	9	
PA	PRA ($\pm$ SD)	0.24 ($\pm$ 0.05)	0.28 ($\pm$ 0.22)	0.720
	PAC ($\pm$ SD)	163.4 ($\pm$ 73.5)	170.4 ($\pm$ 93.6)	0.887
	ARR ($\pm$ SD)	666.1 ($\pm$ 207.3)	1087 ($\pm$ 1188.6)	0.456
	n	53	57	
Non PA	PRA ($\pm$ SD)	3.00 ($\pm$ 4.71)	1.83 ($\pm$ 3.06)	0.123
	PAC ($\pm$ SD)	68.75 ($\pm$ 58.7)	84.34 ($\pm$ 55.1)	0.153
	ARR ($\pm$ SD)	78.22 ($\pm$ 78.6)	113.7 ($\pm$ 112.6)	0.060

The effects were examined in all patients, and in patients with or without PA.

P values were determined using Student's independent-samples *t*-test and were considered to be statistically significant at $P < 0.05$.

ARB, angiotensin II receptor blocker; DM, diabetes mellitus; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PAR, plasma renin activity; ARR, PAC/PRA ratio

Table 5 Clinical profiles of patients with PA with or without DM

	n	DM (Mean $\pm$ S.D)	n	Non DM (Mean $\pm$ S.D)	P value
Sex (male / female)	15	8/7	28	9/19	0.766
Age (yr)	15	66.45 $\pm$ 8.43	28	55.07 $\pm$ 10.53	0.0017
Duration of HT (yr)	10	17.44 $\pm$ 11.28	25	7.55 $\pm$ 9.87	0.018
BMI (kg/m ²)	15	24.7 $\pm$ 2.49	27	22.48 $\pm$ 2.56	0.203
Number of antihypertensive drug	15	1.80 $\pm$ 1.54	28	1.17 $\pm$ 1.25	0.067
Systolic BP (mmHg)	15	141.3 $\pm$ 22.17	28	130.4 $\pm$ 15.25	0.181
Diastolic BP (mmHg)	15	80.00 $\pm$ 15.32	28	80.56 $\pm$ 10.66	0.787
PAC (pg/mL)	15	180.6 $\pm$ 104.6	28	219.3 $\pm$ 167.1	0.310
PRA (ng/mL·hr)	15	0.24 $\pm$ 0.08	28	0.27 $\pm$ 0.14	0.072
ARR	15	822.5 $\pm$ 491.8	28	1080.5 $\pm$ 1523.2	0.981
Cr (mg/dL)	15	0.89 $\pm$ 0.31	28	0.72 $\pm$ 0.18	0.042
eGFR (mL/min/1.73m ²)	15	66.6 $\pm$ 16.9	28	77.10 $\pm$ 19.48	0.106
Na (mEq/L)	15	141.4 $\pm$ 3.85	28	141.7 $\pm$ 1.44	0.355
K (mEq/L)	15	3.82 $\pm$ 0.52	28	3.64 $\pm$ 0.45	0.097
HbA1c (NGSP) (%)	15	7.41 $\pm$ 1.62	15	5.59 $\pm$ 0.17	0.0004
The antihypertensive drug	n	DM (%)	n	Non DM (%)	
ARB	5	(33.3)	8	(28.6)	0.99 ^a
CCB	12	(80)	14	(50)	0.45 ^a
Diuretic drug	1	(6.7)	2	(7.1)	
ACE-I	1	(6.7)	2	(7.1)	
α -blocker	3	(20)	0	(0)	
β -blocker	2	(13.3)	3	(10.7)	
Selective aldosteron blocker	1	(6.7)	1	(3.6)	

P values were determined using Student's independent-samples *t*-test and were considered to be statistically significant at $P < 0.05$. The types of antihypertensive drugs at the time of measurement of ARR in patients with PA with or without DM are also shown. PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, PAC/PRA ratio; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor ^a, statistical value based on Fisher's probability test for the ARR determination between DM and non DM patients.

vs. 7.55 ± 9.87 years) compared with patients without DM. HbA1c was also significantly different between the two groups. By contrast, other factors, including PRA, PAC, and ARR, were not significantly different between patients with and without DM. The effects of hypertensive drugs on ARR were also examined in this population. The types of antihypertensive drugs used at the first measurement of ARR in patients with and without PA are also listed in Table 5. As most of the patients were treated with an ARB and/or CCB, we focused on these classes of antihypertensive drugs. Fisher's analysis revealed no significant effects of ARBs or CCBs on ARR in patients with or without DM. The *P* values in these analyses for the use of ARBs and CCBs were 0.99 and 0.45, respectively (Table 5).

Discussion

PA is characterized by autonomic overproduction of aldosterone. It causes hypertension as well as oxidative stress, including oxidation of low-density lipoproteins and endothelial dysfunction, which promote atherosclerosis [26, 27]. Aldosterone also induces damage in several tissues, including the brain, heart, and kidney [24]. Drugs that inhibit aldosterone activity, such as mineralocorticoid receptor (MR) antagonists (*e.g.*, spironolactone and eplerenone) show beneficial anti-oxidative and anti-atherosclerotic effects [28, 29]. The results of the Randomized Aldactone Evaluation Study (RALES) were particularly remarkable in that the addition of a low dose of spironolactone (25 mg) to an ACE, diuretic, and digitalis was associated with a dramatic (30%) reduction in the overall mortality rate among patients with severe cardiac failure [30]. Accordingly, early diagnosis and treatment of PA is particularly important.

Hypertension in patients with PA was reported to be improved or cured by operative resection of the responsible unilateral adrenal adenoma in most patients [31], supporting the concept that surgical excision of the adenoma should be the first-line therapy, if possible. In patients with non-operable tumors or for those who cannot hope for surgery, antihypertensive drugs are usually used, and remarkable effects from drugs that inhibit aldosterone activity have been reported [32]. Additionally, some dihydropyridine CCBs, such as nifedipine, were reported to possess MR antagonist activity and effectively control BP in patients with PA [33]. Although the coexistence of DM and hyperten-

sion is very common, only three studies have examined the prevalence of PA in such patients in other countries [15-17]. The overall prevalence of PA in patients with both DM and hypertension ranged from 13% to 24% in those studies [15-17]. However, only two of those studies focused on DM patients with resistant hypertension [15, 16]. In the present study, we targeted subjects with DM and unselected hypertension, and found that 11.3% of patients with DM and hypertension actually had PA. Thus, the prevalence of PA in Japanese diabetic patients with hypertension is similar to that observed in other countries.

While many studies have determined the prevalence of PA in unselected hypertensive patients within institutions, the prevalence of PA in hypertensive patients is approximately 3.3–15.0% [2-5]. Therefore, the frequent coexistence of DM and hypertension might prompt clinicians to overlook PA as the most common secondary hypertension. If hypertension in patients with DM is secondary to DM, the prevalence of PA in patients with DM and hypertension may be lower than that in the general hypertensive population. Surprisingly, however, the prevalence of PA in our study and in other studies was almost the same as that in the hypertensive population. According to the National Health and Nutrition Examination Survey in 2003, only 53% of individuals achieved the BP target of 140/90 mmHg [34]. The same study also showed that only 25% of patients with both DM and hypertension achieved the BP target of <130/85 mmHg, indicating the difficulty of controlling hypertension in patients with DM [34]. Resistant hypertension is a condition in which BP cannot be adequately controlled, despite using more than three antihypertensive drugs. In a study of 1616 patients with resistant hypertension, 182 patients (11.6%) were ultimately diagnosed with PA [35]. Based on these findings, it is essential that PA is promptly diagnosed to facilitate appropriate antihypertensive treatment, particularly in patients with resistant hypertension.

It has been suggested that PRA, PAC, and ARR can be affected by several kinds of antihypertensive drugs, sometimes leading to false-positive or false-negative results of screening or diagnostic tests for PA. Antihypertensive drugs that may influence the renin-angiotensin-aldosterone system (RAAS), including ARBs, ACEIs, aldosterone blockers, diuretics, and β -blockers, are not recommended during the screening of PA [1]. Instead, CCBs and α -blockers, which have weaker effects on the RAAS, are recommended

[1]. ARBs and ACEs are commonly used as first-line antihypertensive drugs in patients with DM because of their renoprotective effects and because they alleviate insulin resistance to some extent [18, 24, 25]. In this study, we examined the effects of various antihypertensive drugs, including ARBs on the diagnosis of PA. However, ARR was not significantly affected by the classes of antihypertensive drugs, including ARBs, in patients with or without PA defined as $ARR \geq 200$. Similar results were reported in several studies of general hypertensive populations [36, 37]. Even in one patient with DM and PA who was treated with eplerenone, the ARR was 3840 and all three tests were positive. This case was considered to be typical of PA. Nevertheless, we should not reject the possibility that some of the patients without PA in our study were incorrectly classified based on false-negative results of the tests for PA. Therefore, to reach a definitive conclusion in suspected or borderline patients, reexamination may be necessary after halting the administration of ARBs or ACEIs.

Antidiabetic drugs appear to have very little effect on ARR. To our knowledge, there have been very few reports showing clear effects of SUs, α -GIs, biguanides, and glinides on the RAAS in humans. Intriguingly, pioglitazone was reported to suppress the angiotensin II-induced increase in aldosterone production from cultured H295 adrenocortical cancer cells, which occurred in combination with the suppression of CYP11B2 [38]. However, in patients with DM complicated with coronary disease, 15 mg pioglitazone did not appear to affect the RAAS, as it did not alter PRA or PAC [39]. Although glucagon-like peptide-1 was recently reported to reduce proximal tubular sodium reabsorption, it did not affect PRA or PAC following its administration to young healthy males [40].

The RAAS cascade begins with renin secretion from renal juxtaglomerular cells in response to renal hypoperfusion, decreased sodium delivery, and sympathetic activation. Thus, patients with severe diabetic neuropathy are sometimes thought to have RAAS suppression, characterized by low PRA and PAC levels, because of reduced activity of the sympathetic nervous system [25, 41]. In such circumstances, we must be careful when evaluating the ARR and the results of the loading or suppression tests. In our study, the mean PAC level in patients with PA was 167.9 pg/mL. Because patients with $PAC \geq 150$ pg/mL were strongly suspected of having PA [42], the PAC in our study

seems to indicate autonomic aldosterone secretion. The mean FBS and HbA1c levels in patients with PA were 115.3 mg/dL and 7.26% (NGSP), respectively, suggesting that the diabetic status of these patients was relatively mild. The relatively small effect of DM on the RAAS was unlikely to have a marked impact on the diagnosis of PA in our study. However, we cannot reject the possibility that some false-negative test results led to the incorrect classification of some patients as not having PA. Consequently, we think that the prevalence of PA (11.3%) in patients with DM and hypertension in this study might slightly underestimate the true prevalence of PA.

Two of the 14 patients with DM did not undergo AVS. Although obesity-associated hyperaldosteronism [43] could result in a false-positive diagnosis of PA, it was unlikely in these two patients because their BMI was 19.6 and 23.4 kg/m².

A notable feature of the patients with PA, DM, and hypertension in our study is that they had a relatively shorter history of DM and most were diagnosed with hypertension before DM compared with the patients without PA. Although this was not apparent in all of the patients with PA, these differences were statistically significant based on the results of Fisher's test. If hypertension is secondary to DM, DM should develop either before or at the same time as hypertension. The greater tendency for hypertension to occur before DM in patients with PA rejects this possibility and highlights the relatively independent pathology of hypertension. This sequence of events in patients with PA also suggests that DM may be secondary to PA because PA is well known to induce IGT through various mechanisms [6-10]. Nevertheless, the unique medical history of patients with PA should prompt clinicians to consider the possibility of PA in patients with both DM and hypertension. Among patients with DM and hypertension, the serum potassium, FBS, and HbA1c levels were relatively lower in patients with PA than in those without PA. The lower mean FBS (115.3 mg/dL) and HbA1c (7.26%) levels may also reflect the shorter duration of DM in patients with PA.

In an independent analysis of 43 patients with confirmed PA, we compared the characteristics between those with or without DM. Interestingly, the patients with DM were significantly older and the diagnosis of PA was considerably delayed compared with patients without DM. The delayed diagnosis of PA in patients with DM may be explained by the assumption that

hypertension is probably secondary to DM, when, in fact, PA seems to be much more prevalent than expected among patients with DM and hypertension.

There are several limitations to our study including a relatively small number of the subjects and the fact that we only included hospitalized patients. Additionally, we cannot ignore the possibility of selection bias because some patients with hypertension and DM were not enrolled in this study owing to their general conditions and situations.

In conclusion, we found that 11.3% of patients with DM and hypertension have PA. Among patients with DM, the development of hypertension before DM should prompt clinicians to suspect the possibility of PA as a cause of hypertension. Our results also suggest that there is no need to stop antihypertensive med-

ications to reach the diagnosis of PA, except in suspected/borderline cases requiring reexamination. More extensive screening for PA is highly recommended for patients with both DM and hypertension.

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Disclosure

The authors declare no conflicts of interest relevant to this work.

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