High Prevalence of Diabetes in Patients With Primary Aldosteronism (PA) Associated With Subclinical Hypercortisolism and Prediabetes More Prevalent in Bilateral Than Unilateral PA: A Large, Multicenter Cohort Study in Japan

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OBJECTIVE

To investigate the prevalence and causes of diabetes in patients with primary aldosteronism (PA) in a multi-institutional cohort study in Japan.

RESEARCH DESIGN AND METHODS

The prevalence of diabetes was determined in 2,210 patients with PA (diagnosed or glycated hemoglobin [HbA_{1c}] ≥6.5% [≥48 mmol/mol]; NGSP) and compared with that of the Japanese general population according to age and sex. In 1,386 patients with PA and clear laterality (unilateral or bilateral), the effects of plasma aldosterone concentration (PAC), hypokalemia (<3.5 mEq/L), suspected subclinical hypercortisolism (SH; serum cortisol ≥1.8 μg/dL after 1-mg dexamethasone suppression test), and PA laterality on the prevalence of diabetes or prediabetes (5.7% ≤ HbA_{1c} <6.5% [39 mmol/mol ≤ HbA_{1c} <48 mmol/mol]) were examined.

RESULTS

Of the 2,210 patients with PA, 477 (21.6%) had diabetes. This prevalence is higher than that in the general population (12.1%) or in 10-year cohorts aged 30–69 years. Logistic regression or χ^2 test revealed a significant contribution of suspected SH to diabetes. Despite more active PA profiles (e.g., higher PAC and lower potassium concentrations) in unilateral than bilateral PA, BMI and HbA_{1c} values were significantly higher in bilateral PA. PA laterality had no effect on the prevalence of diabetes; however, the prevalence of prediabetes was significantly higher in bilateral than unilateral PA.

CONCLUSIONS

Individuals with PA have a high prevalence of diabetes, which is associated mainly with SH. The prevalence of prediabetes is greater for bilateral than unilateral PA, suggesting a unique metabolic cause of bilateral PA.

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Primary aldosteronism (PA) is characterized by the autonomous production of aldosterone, usually from an aldosterone-producing adenoma (APA) in one adrenal gland or idiopathic hyperaldosteronism (IHA) with bilateral adrenal lesions. Classically, PA is accompanied by hypertension and hypokalemia because aldosterone works through mineralocorticoid receptors to increase blood pressure by promoting reabsorption of sodium and excretion of potassium by the kidneys (1).

It has been suggested that aldosterone overproduction in patients with PA is related to impaired glucose homeostasis (2) and insulin resistance (3). Insulin resistance is present in patients with PA, and surgical treatment or aldosterone antagonists can restore normal sensitivity to insulin (3). Additionally, a positive correlation between aldosterone concentrations and insulin resistance has been demonstrated in normotensive healthy subjects (4). High concentrations of aldosterone have been shown to predict the development of insulin resistance 10 years later in people without insulin resistance at baseline (5). An example of a mechanism for insulin resistance mediated by aldosterone is aldosterone-induced mineralocorticoid receptor activation, which impairs insulin sensitivity in adipocytes and skeletal muscle (6). Aldosterone may cause insulin resistance indirectly by increasing proinflammatory cytokines and reducing beneficial adipokines such as adiponectin (6,7). Aldosterone can induce failure of clonal pancreatic β-cells through glucocorticoid receptors (8).

Several reports have suggested that hypokalemia is a potential risk factor for diabetes. This suggestion is supported by randomized controlled trials of thiazide diuretics in which serum potassium concentrations were related inversely to glucose, this effect being blunted by oral potassium supplements (9). In healthy people, potassium depletion impairs glucose tolerance because of a delay in the initial phase of insulin secretion, with no evidence of insulin resistance (10).

Another factor that may explain glucose intolerance in patients with PA is subclinical hypercortisolism (SH), also termed subclinical Cushing syndrome (CS), because these two disorders reportedly occur together (11,12). SH or subclinical CS is characterized by subtle autonomous cortisol secretion and an absence of clinical evidence of CS (13). SH is sometimes hidden within "lifestyle diseases" such as obesity, diabetes, hypertension, and cardiovascular disease (14,15).

An overnight 1-mg dexamethasone suppression test (DST) is essential for diagnosing SH; however, the screening criteria are controversial. Japanese diagnostic criteria include three hierarchical cortisol cutoff values, 5.0, 3.0, and 1.8 μg/dL (13). Serum cortisol ≥5 μg/dL after a 1-mg DST alone is considered sufficient to diagnose SH; criteria based on serum cortisol ≥1.8 or ≥3 μg/dL after a 1-mg DST can also be used to make the diagnosis in conjunction with several other conditions (13). A screening serum cortisol concentration of ≥1.8 μg/dL after a 1-mg DST has also been proposed by the Endocrine Society (16) and the European Society of Endocrinology (17).

However, the true contributions of these factors (hyperaldosteronism, hypokalemia, and SH) to disturbances of carbohydrate metabolism in PA have not been investigated thoroughly from a large-scale epidemiologic viewpoint. In the current study, the true prevalence of glucose intolerance in more than 2,000 patients with PA and its association with aldosterone concentration, hypokalemia, and SH were studied in a multicenter collaborative study.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This study was conducted as part of the Japan Primary Aldosteronism Study (JPAS), a multicenter collaborative study in Japan (18). Patients who were diagnosed as having PA and had undergone adrenal venous sampling (AVS) between January 2006 and October 2016 were enrolled. Both men and women aged 20–90 years were eligible for this study. Data in the JPAS database (2,814 individuals with PA from 30 centers as of February 2018) were analyzed retrospectively. The clinical and biochemical findings and the results of the AVS were

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electronically collected using an online registry system; data security was outsourced to EPS (Tokyo, Japan). The study protocol was approved by the ethics committee of the National Hospital Organization Kyoto Medical Center (the project leader center) and by the institutional ethics committees of all participating centers.

In this study, the prevalence and characteristics of disturbed glucose metabolism in patients with PA were investigated along with hypokalemia, aldosterone concentrations, and SH. The effects of hypokalemia (<3.5 mEq/L), plasma aldosterone concentration (PAC), suspected SH diagnosed using a 1-mg DST, and PA laterality (unilateral or bilateral) on glucose intolerance in these patients were investigated.

Of the 2,814 individuals with PA in the original database, 2,210 for whom data on glycated hemoglobin (HbA_{1c}) were available were extracted and the actual prevalence of diabetes in these patients examined. From these 2,210 patients, 1,781 in whom AVS had been successful were selected, after which 1,386 of those patients were selected to examine the effect of laterality of PA (unilateral or bilateral) on the prevalence of diabetes and prediabetes.

Data on patients with PA were also compared with data on the general population from the National Survey of the Ministry of Health, Labour and Welfare (MHLW) in 2016 (19), with the aim of determining the prevalence of diabetes. Of 11,191 control individuals from the National Survey of the MHLW for whom HbA_{1c} values were available, 7,169 aged 30–69 years were extracted and their prevalence of diabetes compared with that in 2,034 patients with PA aged 30–69 years. Age-groups 20–29 years and ≥70 years were excluded because there were too few patients in these age-groups with PA. The prevalence of diabetes in patients with PA was also compared with 245 patients with essential hypertension (EHT) treated between January 2006 and December 2013 in the Kyoto Medical Center cohort. Of the 245 patients with EHT, 230 were age and sex matched with 230 patients with PA, and 218 were matched with 218 patients with PA but without suspected SH. An age-, sex-, and BMI-matched comparison was also performed between patients with EHT and those with PA.

Diagnosis of PA

All patients were diagnosed as having PA according to the guidelines of the Japan Endocrine Society (20) and the Japanese Society of Hypertension (21). This diagnosis was made based on a ratio of PAC (pg/mL) to plasma renin activity (PRA) (ng/mL/h) (aldosterone-to-renin ratio [ARR]) >200 and at least one positive result among the following confirmatory tests: captopril challenge, saline infusion, furosemide upright, and oral salt loading tests. Antihypertensive medications were usually changed to calcium channel blockers or α-adrenergic blockers, as appropriate, until a final diagnosis had been made.

Diagnosis of Glucose Intolerance

Diabetes (or strongly suspected diabetes) was defined as having HbA_{1c} ≥6.5% (48 mmol/mol) (NGSP) or being treated for diabetes diagnosed on the basis of the definition set in a national survey conducted by the MHLW in Japan (19). HbA_{1c} ≥6.5% (48 mmol/mol) is considered to be diagnostic of diabetes according to the criteria set by the American Diabetes Association (ADA) (22), or "diabetic type" according to the criteria set by the Japan Diabetes Society (23). The definition of prediabetes (or categories of increased risk of diabetes) based on HbA_{1c} is somewhat controversial; however, 5.7% ≤ HbA_{1c} <6.5% (39 mmol/mol ≤ HbA_{1c} <48 mmol/mol) is thought to denote prediabetes (22). Thus, patients with PA and 5.7% ≤ HbA_{1c} <6.5% (39 mmol/mol ≤ HbA_{1c} <48 mmol/mol) were defined as having prediabetes in this study. HbA_{1c} <5.7% (39 mmol/mol) was tentatively defined as denoting normal glucose tolerance (NGT) in this study; this is based on the ADA categorization of diabetes and prediabetes (22).

Diagnosis of SH

According to the protocol for an overnight 1-mg DST, 1 mg of dexamethasone is administered orally at 2300 h, and the next morning at 0800 h to 0900 h a fasting blood sample is taken to measure serum cortisol concentration. A screening criterion of serum cortisol ≥1.8 μg/dL after a 1-mg DST was used to make a tentative diagnosis of suspected SH (13,16,17). In this multicenter collaborative study, it was difficult to make a certain diagnosis of SH because of a lack of the required confirmatory data. Serum cortisol (F) ≥1.8 μg/dL after a 1-mg DST (expressed as F 1-mg DST ≥1.8 μg/dL) and serum cortisol <1.8 μg/dL after a 1-mg DST (expressed as F 1-mg DST <1.8 μg/dL) were used to diagnose suspected SH and nonsuspected SH (normal), respectively.

PA Laterality (Subtype) Diagnosis

AVS is essential for determining laterality (unilateral or bilateral) in patients with PA, as described previously (24). ACTH (cosyntropin) was administered as a bolus injection, a bolus injection followed by continuous infusion, or continuous infusion only. AVS after ACTH loading was defined as successful if the selectivity index, defined as the ratio of the cortisol concentration in the adrenal vein to that in the inferior vena cava, was >5 (25,26). Patients in whom AVS had not been performed, those with unsuccessful AVS based on the above definition, and those with no ACTH loading in AVS were excluded, leaving 1,781 patients with PA and successful AVS. The unilateral subtype of PA, APA, was diagnosed when the lateralized ratio (LR; calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side) was >4 and the contralateral ratio (calculated by dividing the aldosterone-to-cortisol ratio on the nondominant side by that in the inferior vena cava) was <1 after ACTH loading (25,27). The bilateral subtype of PA, including IHA, was diagnosed when LR <2. When LR ranged from 2 to 4, patients were diagnosed as having an undetermined subtype of PA and excluded from our comparative analysis to avoid uncertainty about the laterality effect. On the basis of the above strict definitions, 505 patients with unilateral and 881 with bilateral PA (1,386) were ultimately included in the determination of effect of laterality on glucose intolerance.

Assay Methods

PACs were measured using a commercially available radioimmunoassay (SPAC-S Aldosterone Kit; Fuji Rebio, Tokyo, Japan) at all centers. The reference range for PACs with patients in a supine position was 30–159 pg/mL. PRA was measured using various radioimmunoassay (RIA) or enzyme immunoassay (EIA) kits. The reference ranges for PRA in a supine position were almost the same: 0.3–2.9 ng/mL/h

(PRA-FR RIA Kit; Fuji Rebio), 0.2–2.3 ng/mL/h (PRA EIA Kit; Yamasa, Choshi, Japan), and 0.2–2.7 ng/mL/h (PRA RIA Kit; Yamasa). Cortisol concentrations were measured using an electrochemiluminescence immunoassay (Roche, Tokyo, Japan) at 19 centers, a chemiluminescent immunoassay (Siemens Healthineers, Tokyo, Japan) at four centers, an EIA (TOSOH, Tokyo, Japan) at four centers, and a chemiluminescent enzyme immunoassay (CLEIA) (Beckman Coulter, Tokyo, Japan) at three centers. Their coefficients of variation are <15%, with the exception of the CLEIA, which is <12%. The ranges of measurement of these kits are 0.054–63.4, 0.50–75.0, 0.2–60.0, and 0.4–60.0 μg/dL, respectively.

Statistics

All data are expressed as the mean ± SD for normally distributed variables and as the median (25th–75th percentile) for nonnormally distributed variables. Student *t* test or the Mann-Whitney *U* test was used for quantitative valuables. The χ^2 test was used to compare frequencies. Logistic regression analysis was performed to determine the effect of variables on glucose intolerance. Statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY), and $P < 0.05$ was considered to denote significance.

RESULTS

The characteristics of the 2,210 patients with PA and HbA_{1c} data are shown in Supplementary Table 1. The average age was 53.5 ± 11.1 years, there were 1,076 men and 1,134 women, and the average BMI was 24.9 ± 4.2 kg/m^2. Of these 2,210 patients, 477 (21.6%) met the criteria for diabetes (previously diagnosed or HbA_{1c} ≥6.5%). There were 628 patients (28.4%) with prediabetes (5.7% ≤ HbA_{1c} <6.5%) and 1,105 (50%) with NGT (HbA_{1c} <5.7%). The prevalence of diabetes (21.6%) in patients with PA was unchanged when the number of patients decreased according to the purpose of the study analysis, as described below, 379 of 1,781 (21.3%) in whom AVS was successful and 278 of 1,386 (20.1%) with clear laterality, suggesting that the proportion of patients with PA who have diabetes was not affected by data selection.

An attempt was made to compare the prevalence of diabetes in patients with PA with that in the general population in Japan (19); the same criteria were used to define diabetes in both sets of data. The overall prevalence of diabetes was 12.1% of the general Japanese population aged ≥20 years in that survey. Furthermore, an attempt was made to compare the prevalence of diabetes in patients with PA according to 10-year age-groups of men and women separately with that in the corresponding sector of the general population (19). From the total sample (*n* = 11,191) of the general population, 7,169 people (2,845 men and 4,324 women, aged 30–69 years) were extracted. Similarly, 2,034 patients with PA (998 men and 1,036 women, aged 30–69 years) were extracted. As indicated in Supplementary Table 2, the prevalence of diabetes was higher in all age-groups (30–39 years, 40–49 years, 50–59 years, and 60–69 years) of patients with PA than in the general population ($P < 0.01$ for both men and women) (Supplementary Table 2).

The prevalence of diabetes in patients with PA was also compared with that in patients with EHT in the Kyoto Medical Center cohort by matching for age and sex (*n* = 230, male/female = 126/104, and age 58.9 ± 12.0 years in each group). A higher prevalence of diabetes was identified in the 230 patients with PA than in the 230 with EHT (24.3% vs. 14.3%, $P = 0.007$); additionally, the BMI was higher in individuals with PA than in those with EHT (24.7 ± 3.9 vs. 23.9 ± 3.4 kg/m^2, $P = 0.028$). In the comparison matching for age, sex, and BMI, there was no significant difference in the prevalence of diabetes between the PA group (*n* = 221) and the EHT group (*n* = 221) (21.7% vs. 14.9%, $P = 0.085$). Importantly, when matched for age and sex, there was also no significant difference in the prevalence of diabetes between the 218 patients with PA but without suspected SH and the 218 patients with EHT (21.1% vs. 14.2%, $P = 0.060$).

Factors that were significantly associated with the prevalence of diabetes were identified using logistic regression analysis (Supplementary Table 3). The presence of hypokalemia (K <3.5 mEq/L) and PAC were not significant contributing factors; however, F 1-mg DST ≥1.8 μg/dL, age, and BMI did significantly affect the prevalence of diabetes ($P < 0.001$).

For the 1,386 patients in whom successful AVS had enabled differentiation between unilateral and bilateral PA, the prevalence of diabetes was compared between the two types of PA. The basic characteristics of these 1,386 patients were compared according to laterality of PA (unilateral, *n* = 505; bilateral, *n* = 881) (Table 1). Individuals with unilateral PA had more active disease, as evidenced by relatively higher PAC and ARRs and lower PRAs and serum potassium concentrations, than those with bilateral PA (all $P <$ 0.001) (Table 1). However, HbA_{1c} values were significantly higher in those with bilateral PA (5.7%; range 5.4–6.0%) than in those with unilateral PA (5.5%; range 5.2–5.9%) (Table 1). Additionally, the BMI was significantly higher (25.0 ± 4.1 kg/m^2) in individuals with bilateral PA than in those with unilateral PA (24.4 ± 4.2 kg/m^2). These results suggest that PAC and hypokalemia are not associated with higher HbA_{1c} values in patients with bilateral PA than in those with unilateral PA.

According to the χ^2 test, the prevalence of diabetes in the 1,386 study patients did not differ significantly between those with unilateral PA (18.8%) versus bilateral PA (20.8%) (Table 2, left). In the 890 of 1,386 patients for whom F 1-mg DST was available, diabetes was present significantly more frequently in those with suspected SH (26.8%) than in those with F 1-mg DST <1.8 μg/dL (16.9%; $P = 0.001$) (Table 2, left). The presence or absence of suspected SH was not associated with a statistically significant difference in diabetes prevalence between those with unilateral versus bilateral PA (Table 2, left). Factors affecting the presence of diabetes were investigated using logistic regression analysis, and it was found that age, sex, BMI, and F 1-mg DST ≥1.8 μg/dL were significant contributing factors, whereas laterality of PA was not a significant factor (Supplementary Table 4). These results support those of the χ^2 test.

The same comparative analysis was performed for individuals without diabetes (Table 2, right). The presence or absence of suspected SH was not significantly associated with a difference in the prevalence of NGT and prediabetes ($P = 0.287$). However, there was a significantly higher prevalence of prediabetes (41.3%) in individuals with bilateral PA than in those with unilateral PA (30.5%; $P < 0.001$). Prediabetes had a higher prevalence in individuals with bilateral

Table 1—Patient characteristics according to laterality of PA

	Total	Unilateral	Bilateral	*P* value
n	1,386	505	881	
Age (years)	53.1 ± 11.3	52.9 ± 11.9	53.2 ± 11.0	0.594
Sex	M 656/F 730	M 277/F 228	M 379/F 502	<0.001
BMI (kg/m^2)	24.8 ± 4.2	24.4 ± 4.2	25.0 ± 4.1	0.018
SBP (mmHg)	139 (128–151)	140 (130–153)	139 (128–150)	0.022
DBP (mmHg)	86 (78–94)	86 (78–93)	85 (77–95)	0.992
Na (mEq/L)	142 (141–143)	143 (141–144)	142 (140–143)	<0.001
K (mEq/L)	3.8 (3.4–4.0)	3.3 (2.9–3.7)	3.9 (3.7–4.1)	<0.001
Cr (mg/dL)	0.71 (0.60–0.86)	0.75 (0.60–0.92)	0.70 (0.60–0.80)	<0.001
eGFR (mL/min/1.73 m^2)	77.8 ± 20.0	77.1 ± 22.3	79.8 ± 18.5	0.013
TC (mg/dL)	192.8 ± 32.7	188.4 ± 31.5	195.2 ± 33.2	0.001
TG (mg/dL)	106 (76–152)	101 (71–144)	110 (80–158)	0.001
HDL-C (mg/dL)	53 (44–65)	53 (44–65)	53 (45–64)	0.747
FPG (mg/dL)	98 (91–109)	97 (89–109)	99 (92–109)	0.047
HbA_{1c} (%)	5.6 (5.3–6.0)	5.5 (5.2–5.9)	5.7 (5.4–6.0)	<0.001
PAC (pg/mL)	186 (128–307)	322 (209–480)	149 (113–205)	<0.001
PRA (ng/mL/h)	0.30 (0.20–0.50)	0.20 (0.10–0.40)	0.46 (0.20–0.56)	<0.001
ARR	587 (328–1,240)	1,333 (650–2,780)	413 (282–723)	<0.001
F 1-mg DST (μg/dL)	1.2 (0.8–1.7)	1.3 (0.9–1.9)	1.1 (0.8–1.5)	<0.001

Data are shown as the mean ± SD, median (25th–75th percentiles), or raw numbers. *P* value: unilateral vs. bilateral PA. Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; F, female; FPG, fasting plasma glucose; HDL-C, HDL cholesterol; M, male; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

PA than in those with unilateral PA when F 1-mg DST <1.8 μg/dL ($P < 0.001$), but the difference was not significant for suspected SH ($P = 0.679$) (Table 2, right).

Logistic regression analysis was performed to determine the factors affecting the presence of prediabetes (Table 3). Laterality of PA (bilateral) was significantly associated with the presence of prediabetes ($P = 0.033$), whereas PAC, hypokalemia, and suspected SH were not. These results support those of the χ^2 test (Table 2, right). When the 1,386 study patients were divided into two groups according to F 1-mg DST findings, those with F 1-mg DST <1.8 μg/dL and bilateral PA were found to be significantly older, more frequently female, and to have higher BMI, triglycerides, and HbA_{1c} than those with unilateral PA (Table 4).

CONCLUSIONS

The true prevalence of abnormal glucose metabolism and the roles of aldosterone, hypokalemia, and complicated SH in glucose metabolism have not previously been investigated thoroughly in a large cohort of individuals with PA. The effects of PA laterality on BMI and diabetes have been investigated in several small studies, the results of which are controversial (2,28–31). The current JPAS study included a larger number of patients with PA in whom laterality had been accurately determined by AVS.

In the current study, the prevalence of diabetes was higher in patients with PA than it is in the general population; this held true for all 10-year subgroups aged between 30 and 69 years and for both men and women. Because it has been established that hypertension is causally associated with diabetes (32–34), age- and sex-matched cohorts of 230 patients with PA and 230 with EHT were compared; a significantly higher prevalence of diabetes was found in those with PA than in those with EHT. However, no such significant difference was identified when PA patients matched for BMI or without suspected SH were compared with patients with EHT. These results suggest that individuals with PA are prone to developing diabetes independent of age and sex, but dependent on BMI or SH. Interestingly, a population study of 23 million found that over a 5-year follow-up, patients with PA who had not undergone adrenalectomy were at higher risk of new-onset diabetes than those with EHT (35).

In our study, among patients with PA, the prevalence of diabetes was not significantly associated with hypokalemia or PAC values; however, it was associated with suspected SH. We found that 27.4% of our study patients had suspected SH, when the diagnostic criterion was based on F 1-mg DST ≥1.8 μg/dL. On the basis of the results of a mass spectrometry–based analysis of the 24-h urine steroid metabolome in 174 patients with PA, Arlt et al. (14) identified the concomitant presence of glucocorticoid excess in a large proportion of these patients. These results together with our data

Table 2—Effect of SH and laterality of PA on glucose tolerance (χ^2 test)

	All			Patients without diabetes		
	HbA_{1c} <6.5%	HbA_{1c} ≥6.5% or diagnosed diabetes	*P* value	HbA_{1c} <5.7%	HbA_{1c} 5.7–6.4%	*P* value
F 1-mg DST <1.8 μg/dL	566 (83.1)	115 (16.9)	0.001	347 (61.3)	219 (38.7)	0.287
F 1-mg DST ≥1.8 μg/dL	153 (73.2)	56 (26.8)		101 (66.0)	52 (34.0)	
Unilateral	410 (81.2)	95 (18.8)	0.381	285 (69.5)	125 (30.5)	<0.001
Bilateral	698 (79.2)	183 (20.8)		410 (58.7)	288 (41.3)	
F 1-mg DST <1.8 μg/dL & unilateral	233 (85.3)	40 (14.7)	0.212	168 (72.1)	65 (27.9)	<0.001
F 1-mg DST <1.8 μg/dL & bilateral	333 (81.6)	75 (18.4)		179 (53.8)	154 (46.2)	
F 1-mg DST ≥1.8 μg/dL & unilateral	83 (74.1)	29 (25.9)	0.752	56 (67.5)	27 (32.5)	0.679
F 1-mg DST ≥1.8 μg/dL & bilateral	70 (72.2)	27 (27.8)		45 (64.3)	25 (35.7)	

Data are shown as *n* (%).

Table 3—Effects of selected variables on the difference between NGT (HbA_{1c} <5.7%) and prediabetes (5.7% ≤ HbA_{1c} <6.5%) after adjusting for age, sex, and BMI

Variables	Odds ratio	95% CI	*P* value
Age	1.057	1.039–1.076	<0.001
Sex (male = 1, female = 2)	1.890	1.248–2.863	0.003
BMI	1.085	1.031–1.142	0.002
Hypokalemia (hypokalemia = 1, eukalemia = 2)	0.994	0.975–1.013	0.540
TC	1.004	0.998–1.011	0.191
TG	1.003	1.000–1.006	0.086
HDL-C	0.989	0.974–1.004	0.147
PAC	0.999	0.998–1.000	0.100
F 1-mg DST (<1.8 = 1, ≥1.8 = 2)	0.964	0.597–1.556	0.881
Localization of PA (unilateral = 1, bilateral = 2)	1.603	1.038–2.477	0.033

HDL-C, HDL cholesterol; TC, total cholesterol; TG, triglyceride.

suggest that patients with PA have an increased risk of high glucocorticoid concentrations.

The pathogenesis of aldosterone overproduction in bilateral PA, including IHA, may be related to obesity and insulin resistance. Secretory products from isolated human adipocytes stimulate aldosterone secretion in human adrenocortical NCI-H295R cells, suggesting that human adipocytes secrete aldosterone-releasing factors (36,37). Additionally, hyperinsulinemia in obesity is attributable to increased sympathetic nerve activity that activates the renin-angiotensin-aldosterone system (31,38). On the basis of these findings, metabolic phenotypes of IHA and APA have been compared. Recent retrospective studies by Somlóová et al. (28) and Matrozova et al. (29), who investigated 100 patients with PA (50 IHA and 50 APA) and 460 patients with PA (150 IHA, 103 APA, and 207 undetermined type), respectively, showed significantly higher BMIs in the IHA than the APA group and that the prevalence of diabetes did not differ between the two groups. These findings are consistent with ours. However, Fallo et al. (2) and Rossi et al. (30) reported no difference in BMI between 29 patients with APA and 56 with IHA and between 54 with APA and 72 with IHA, respectively. The precise reason for these discrepancies is unclear; however, differences in the criteria for identifying PA subtype, especially bilateral PA (IHA), or in sample size may have been contributing factors.

In our study, the prevalence of diabetes did not differ between individuals with unilateral versus bilateral PA. Given that individuals with bilateral PA are at high risk of obesity, we considered it important to also investigate prediabetes (2,28–31). We found that prediabetes was significantly more prevalent in patients with bilateral PA than in those with unilateral PA. This difference was identified under the only condition of F 1-mg DST <1.8 μg/dL, suggesting that suspected SH is not responsible for the predominance of prediabetes in individuals with bilateral PA. As previously reported (31), individuals with unilateral PA had higher PACs and a greater prevalence of hypokalemia than those with bilateral PA, suggesting that PAC and hypokalemia are not associated with laterality in individuals with prediabetes. The precise reason for the higher prevalence of prediabetes in individuals with bilateral PA remains unknown. However, our results suggest several contributing

Table 4—Characteristics of patients with unilateral and bilateral PA according to serum *F* values after 1-mg DST

	F 1-mg DST <1.8 μg/dL			F 1-mg DST ≥1.8 μg/dL		
	Unilateral (*n* = 273)	Bilateral (*n* = 408)	*P* value	Unilateral (*n* = 112)	Bilateral (*n* = 97)	*P* value
Age	51.0 ± 12.4	53.2 ± 11.0	0.018	57.7 ± 10.1	56.8 ± 10.9	0.551
Sex	M 145/F 128	M 181/F 227	0.025	M 58/F 54	M 40/F 57	0.128
BMI (kg/m^2)	24.4 ± 4.4	25.4 ± 4.2	0.007	24.1 ± 4.0	24.0 ± 3.9	0.910
SBP (mmHg)	140 (129–151)	138 (126–149)	0.088	140 (128–155)	140 (129–156)	0.870
DBP (mmHg)	86 (78–93)	85 (76–95)	0.606	86 (78–92)	88 (78–95)	0.458
Na (mEq/L)	143 (141–144)	142 (140–143)	<0.001	144 (142–145)	142 (140–143)	<0.001
K (mEq/L)	3.3 (2.9–3.6)	3.9 (3.7–4.1)	<0.001	3.4 (2.8–3.7)	3.8 (3.6–4.1)	<0.001
Cr (mg/dL)	0.73 (0.59–0.90)	0.70 (0.59–0.80)	0.016	0.80 (0.62–0.93)	0.71 (0.59–0.86)	0.051
eGFR (mL/min/1.73 m^2)	80.4 ± 21.7	80.7 ± 17.8	0.805	71.1 ± 23.5	74.8 ± 18.1	0.272
TC (mg/dL)	190.1 ± 32.3	193.9 ± 33.5	0.173	186.6 ± 28.9	194.2 ± 33.4	0.111
TG (mg/dL)	100 (71–143)	113 (81–155)	0.015	106 (71–143)	106 (87–165)	0.104
HDL-C (mg/dL)	52 (45–64)	52 (44–63)	0.517	54 (44–67)	54 (45–64)	0.997
FPG (mg/dL)	96 (89–106)	98 (91–108)	0.076	101 (91–115)	100 (93–109)	0.515
HbA_{1c} (%)	5.5 (5.2–5.8)	5.7 (5.4–6.0)	<0.001	5.6 (5.3–6.2)	5.7 (5.4–6.2)	0.321
PAC (pg/mL)	318 (215–492)	148 (113–216)	<0.001	388 (214–539)	177 (121–249)	<0.001
PRA (ng/mL/h)	0.2 (0.1–0.4)	0.3 (0.2–0.6)	<0.001	0.3 (0.1–0.4)	0.4 (0.2–0.6)	0.001
ARR	1,345 (638–2,810)	433 (270–752)	<0.001	1,346 (640–3,180)	457 (307–778)	<0.001
F 1-mg DST (μg/dL)	1.0 (0.8–1.3)	1.0 (0.7–1.2)	0.054	2.5 (2.0–3.8)	2.5 (2.0–3.8)	0.902

Data are shown as mean ± SD, median (25th–75th percentiles), or raw numbers. Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; F, female; FPG, fasting plasma glucose; HDL-C, HDL cholesterol; M, male; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

factors, namely the older age and higher BMI and triglycerides in patients with bilateral PA, as has also been suggested by previous researchers (36,37). These characteristics of bilateral PA suggest the presence of insulin resistance, which confers susceptibility to prediabetes. A unique and as yet unknown mechanism may be responsible for prediabetes in individuals with bilateral PA. Further investigation is needed to clarify the mechanism.

The current study had some limitations. First, the prevalence of diabetes may have been affected by the sample size, and the numbers of patients in some of the subgroups analyzed were small. Second, all data were collected before treatment of PA because the database was not large enough to collect post-treatment data. In individual patients, an improvement in glucose intolerance would be expected in association with changes in serum potassium concentrations or improvement in SH after adrenalectomy. This requires future investigation. Third, although the overnight 1-mg DST was mostly performed during hospitalization, in some cases it was performed at outpatient clinics. This slight difference in protocol raises the possibility that a few patients may have had false-positive data. Furthermore, as to the diagnosis of SH, confirmatory data were not available from this database, limiting the estimation of the contribution of SH.

In conclusion, individuals with PA have a relatively higher prevalence of diabetes, and it is associated with SH. However, prediabetes is more prevalent in patients with bilateral PA than in those with unilateral PA, suggesting a unique metabolic cause in bilateral PA.

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