

Sex-specific Association of Primary Aldosteronism With Visceral Adiposity

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Abstract

Context: The association between primary aldosteronism and obesity, especially its sex difference, remains unknown.

Objective: To assess the association for each subtype of primary aldosteronism with obesity parameters including visceral adipose tissue and differences between sexes.

Methods: In this case-control study, 4 normotensive controls were selected for each case with primary aldosteronism. Multivariable conditional logistic regression models were used to estimate the association between each type of primary aldosteronism and obesity indicators. We used a random forest to identify which visceral or subcutaneous tissue areas had a closer association with disease status.

Results: The study subjects included 42 aldosterone-producing adenoma cases (22 women) and 68 idiopathic hyperaldosteronism cases (42 women). In multivariable conditional logistic regressions, aldosterone-producing adenoma was significantly associated with body mass index only in men (odds ratio [OR] [95% CI]), 4.62 [1.98-10.80] per 2.89 kg/m²) but not in women (OR [95% CI], 1.09 [0.69-1.72] per 3.93 kg/m²) compared with the matched controls, whereas idiopathic hyperaldosteronism was associated with body mass index in both men (OR [95% CI], 3.96 [2.03-7.73] per 3.75 kg/m²) and women (OR [95% CI], 2.65 [1.77-3.96] per 3.85 kg/m²) compared with the matched controls. In random forests, visceral adipose tissue areas were the better predictor of both aldosterone-producing adenoma and idiopathic hyperaldosteronism than subcutaneous adipose tissue.

Conclusions: Aldosterone-producing adenoma cases were obese among men, but not among women. Idiopathic hyperaldosteronism cases were obese among both men and women. Visceral adipose tissue may contribute to the pathophysiology of primary aldosteronism.

Key Words: aldosterone-producing adenoma, idiopathic hyperaldosteronism, obesity, primary aldosteronism, sex difference, visceral adipose tissue.

Abbreviations: APA, aldosterone-producing adenoma; ARR, plasma aldosterone to plasma renin activity ratio; AUC, area under the curve; BMI, body mass index; CT, computed tomography; HDL, high-density lipoprotein; IHA, idiopathic hyperaldosteronism; IQR, interquartile range; PA, primary aldosteronism; PAC, plasma aldosterone; PRA, plasma renin activity; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

Primary aldosteronism (PA) is the most frequent form of secondary hypertension, with a prevalence of 5% to 15% in all hypertensive patients [1, 2]. The 2 predominant causes of PA are aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA) [3, 4]. Patients with PA have a higher prevalence of cardiovascular events and mortality than patients with essential hypertension [4-7]. Primary aldosteronism is a major public health issue given the increase in its

prevalence [8]. There is therefore a pressing unmet need to identify the mechanisms of PA to drive preventative initiatives and improve health outcomes.

Although the increase in its prevalence is most likely a reflection of active screening and surveillance of at-risk patients, other environmental factors such as the substantial increase in the prevalence of obesity could be related to its development [9, 10]. A prior study suggested that the

Received: 7 March 2022. Editorial Decision: 22 June 2022. Corrected and Typeset: 8 July 2022

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prevalence of obesity was significantly higher in patients with IHA than in patients with essential hypertension [11]. However, other studies found no significant association between PA and obesity [12-14]. These studies used subjects with essential hypertension, which is also significantly associated with obesity, as controls. This could mask the association between PA and obesity [15]. Therefore, it is necessary to compare PA cases with normotensive controls who have standard obesity parameters to determine whether PA is associated with obesity.

Ohno et al suggested that patients with IHA were more obese than those with APA [11]. In addition, a difference between sexes has been reported; body mass index (BMI) was significantly higher in IHA patients compared with APA among women, but not among men [16]. However, it remains uncertain whether the association between each subtype of PA and obesity differ by sex compared with non-PA cases. Elucidating the sex-specific association may clarify the underlying mechanisms of PA.

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are different in their patterns of molecular properties and their roles in the regulation of whole-body metabolism [17-20]. Abdominal VAT is considered to be the more pathogenic fat depot because of stronger associations with most cardiometabolic risk factors compared with SAT [21, 22]. A prior study reported a positive association of plasma aldosterone (PAC) with visceral fat area among IHA cases [23]. However, this is limited only among PA cases; it did not include any control groups. To the best of our knowledge, there have been no previous studies comparing the distribution of adipose tissue between PA cases and control groups. We hypothesized that VAT area had a closer association with each subtype of PA than SAT area because patients with PA have a high prevalence of cardiovascular events [4-7]. However, conventional generalized linear model may not be appropriate because of multicollinearity between BMI, VAT, and SAT areas. Thus, we used a random forest, a machine learning algorithm, which can minimize the effect of multicollinearity [24].

Using a dataset of PA patients and health checkup participants whose adipose tissue areas were measured by computed tomography (CT), we assessed (1) whether obesity parameters, including VAT area, were associated with each type of PA; (2) whether the associations differed by sex; and (3) which of the VAT and SAT areas had a closer association with each type of PA.

Materials and Methods

Study Population and Design

In this case-control study, we recruited 183 patients with PA who were diagnosed and underwent adrenal vein sampling at the Jichi Medical University Hospital, the largest academic center in Japan's Tochigi prefecture, during the 14-year period between January 2006 to July 2020. Reference control data were obtained from the master database including Japanese individuals who participated in general health checkups at the Jichi Medical University Health Care Center.

The study was approved by the Ethics Committee of Jichi Medical University. All patients and controls provided informed consent (<http://www.jichi.ac.jp/encd/pdf/20190410.pdf>).

Ascertainment of Cases With PA and Subtype of PA

The diagnostic procedure for PA and its subtype was performed according to the Japan Endocrine Society [25] and the Japan Society of Hypertension [26]. The diagnosis of PA was confirmed when at least 1 of 3 confirmatory tests, such as the captopril challenge test, saline infusion test, or upright-furosemide loading test, was positive [25, 26]. Differentiation between bilateral and unilateral PA was obtained by adrenal vein sampling [25]. The unilateral PA subtype was defined when lateralized ratio was more than four [25, 27, 28]. Then, unilateral APA was diagnosed for those whose pathological result was concordant with a classical histology (ie, aldosterone-producing adrenal cortical adenoma or aldosterone-producing nodule), but not with a nonclassical histology (ie, suspected multiple aldosterone-producing nodule/micronodule nor aldosterone-producing diffuse hyperplasia) [29]. Classical histopathology represents a solitary neoplasm or nodule composed of clear cells, compact eosinophilic cells, or a mixture of both by hematoxylin-eosin staining [29]. The bilateral PA subtype or IHA was diagnosed when the lateralized ratio was < 2 and the contralateral ratio was ≥ 1 [25, 27, 28]. Details are described in the online Data Supplement [30].

Control Selection and Matching

For the current analyses, we selected records of 2594 normotensive participants from health checkups as a control group (systolic blood pressure < 140 mm Hg, diastolic blood pressure < 90 mm Hg, and not taking antihypertensive medication) whose VAT and SAT areas were measured by CT at least 1 time between 2006 and 2018.

To avoid arbitrarily extracting data and to ensure the validity, we created 2 data sets for the normotensive participants using these records in which repetitive participants were included. One of them was created by randomly choosing the date of each individual health checkup, which was used for primary analysis. The other data were created for sensitivity analysis, choosing the initial day of each individual health checkup (Fig. 1). Then, for each case with PA, 4 controls were selected without replacement using nearest-neighbor matching with a Mahalanobis distance function to identify the closest matches in each data set [31]. The characteristics used in identifying potential matches involved these following potential confounders: sex, age, current smoking status, and drinking status. These covariates, which can affect both the prevalence of the disease and obesity, were selected a priori [11, 16]. Blood pressure was not selected as the covariate, as it was considered a collider, but not a confounder, between disease status and obesity parameters [32]. If the collider was controlled for, collider stratification bias would arise [32].

Covariates and Other Variables

All patients and health checkup participants underwent a routine physical examination, evaluation of demographic characteristics (age and sex), habitual status (current smoking status and alcohol consumption), medical history (duration of hypertension, prevalence of diabetes mellitus, history of cardiovascular diseases), medications, vital signs, and weight assessment. BMI was defined as weight divided by height squared (kg/m^2). Blood was collected after an overnight fast among both cases and health checkup participants. Serum cortisol at 8 am, PAC, and plasma renin activity (PRA)

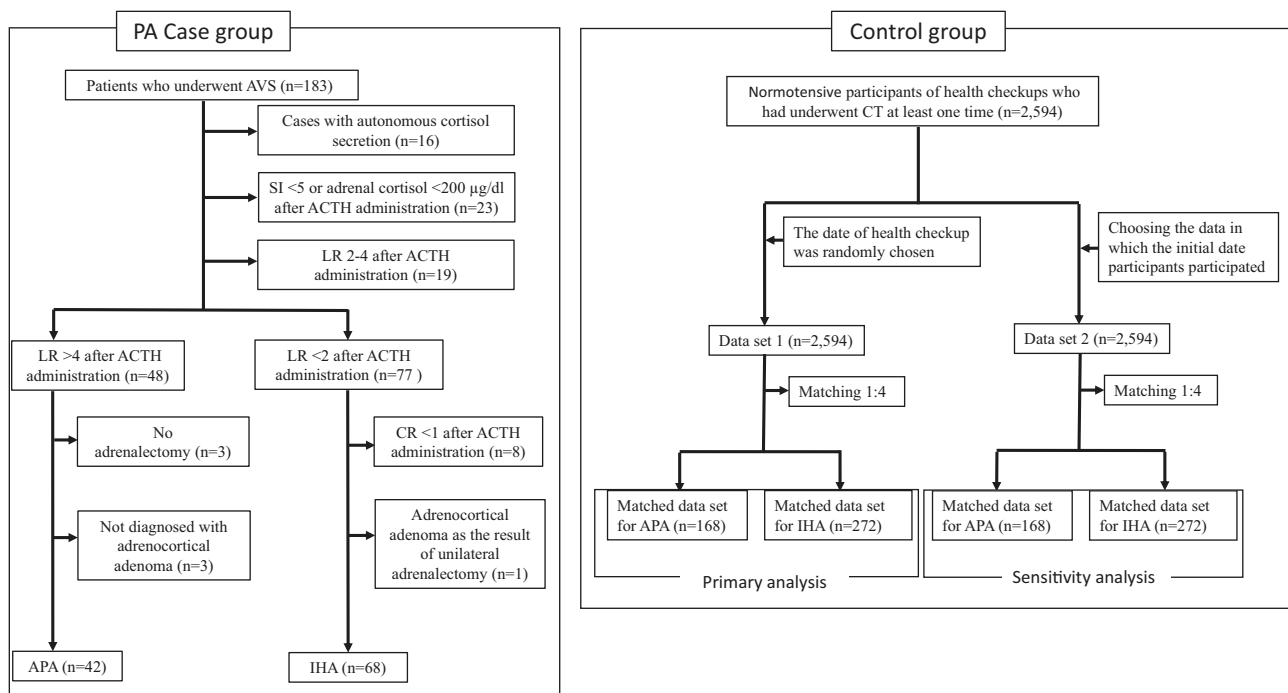


Figure 1. The flow chart of data collection. ACTH, adrenocorticotrophic hormone; APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; CR, contralateral ratio; CT, computed tomography; IHA, idiopathic hyperaldosteronism; LR, lateralized ratio; PA, primary aldosteronism; SI, selectivity index.

were also collected for patients with PA (see the online Data Supplement) [30].

CT Imaging of Abdominal Adipose Tissue

The abdominal adipose tissue imaging was performed in a supine position using a multidetector CT system. Visceral adipose tissue was defined as adipose tissue located within the abdominal muscular wall. Adipose tissue outside the abdominal wall was regarded as SAT. VAT and SAT areas were evaluated at the level just below the kidneys between the third and fourth lumbar vertebrae [33, 34]. Adipose tissue was detected based on attenuation number, using a window level of -200 to -30 Hounsfield units (see the online Data Supplement) [30].

In a preliminary analysis, VAT or SAT areas were found to be highly correlated with BMI, with Pearson's correlation coefficients of 0.75 and 0.81, respectively, for males, and 0.76 and 0.80, respectively, for females (all P values < 0.001). To investigate whether the VAT and SAT areas were associated with the disease status independently of BMI, residuals were calculated based on Willett and Stampfer's residual approach [35]. The residuals represented the proportion of VAT or SAT areas that were not explained by BMI [36]. Details are described in the online Data Supplement [30].

Statistical Analyses

We calculated characteristics for cases and controls. Descriptive statistics are reported as means (SD), medians (interquartile range [IQR]) for skewed variables, and proportions where appropriate. The statistical significance of differences among the groups were determined using independent t tests or Mann-Whitney tests for continuous variables, and χ^2 tests for categorical variables. Correlations between the anthropometric parameters associated with obesity (BMI,

VAT area, and SAT area) and adrenal hormone levels (PAC, PRA, PAC to PRA ratio [ARR], and serum cortisol) were assessed among each type of PA using Pearson's correlation coefficients.

We analyzed the matched patients (ie, APA vs control or IHA vs control) using conditional logistic regression [37]. Standard logistic regression model was used to assess the association of the obesity parameters with APA or IHA. Disease status was put into the models as the dependent variables. In model 1, BMI was considered as the main independent variable. VAT area, SAT area, and both were regarded as the main independent variables in models 2, 3, and 4, respectively. In model 5, BMI and residuals of VAT and SAT areas were included. Sex, age, smoking, and drinking status were adjusted as potential confounders in all models. Results were reported as the adjusted odds ratios for each SD higher level for each exposure. In a sensitivity analysis, we performed the same analysis using the data of each individual's initial day for health checkup participation.

To understand which of the VAT and SAT areas had a closer association with each type of PA, we used several statistical approaches taking multicollinearity into account. First, fitting several models to assess the association as described previously. Second, the differences of area under the receiver operating characteristic curves (AUC) to predict diseases status were calculated for model 2 compared with model 3. Third, variable importance was measured using random forest.

We tested for heterogeneity in the association between PA subtype and obesity parameters by sex via the inclusion of multiplicative interaction terms in models 1 to 3. Statistical analyses were performed using R for Windows, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). The "MatchIt" package in R was used to perform

nearest-neighbor matching. For the random forest, the “randomForest” package in R was used [24]. The number of trees was set to 5000 to ensure robustness of variable importance. For 95% CIs of AUC and the difference in AUC, we used a nonparametric bootstrap approach with 5000 iterations. Statistical significance was defined by a 2-sided *P* value < 0.017 according to Bonferroni correction resulting from multiple comparison tests [38]. In the same way, we used *P* < 0.017 for interpretation of statistical interactions.

Results

Of the 183 cases diagnosed with PA who underwent adrenal vein sampling, we excluded 73 cases that met the exclusion criteria (Fig. 1). We included 110 PA patients (mean age \pm SD, 51.5 years \pm 9.8, and 64 women [58.2%]) who were categorized as having APA (*n* = 42) and IHA (*n* = 68).

Comparisons of Patients With APA and Controls

Comparisons of parameters between patients with APA and the matched controls are shown in Table 1. Age (50.9 \pm 11.2 years), sex (22 [52.4%] women), smoking (6 [14.3%] current smokers), and drinking status (10 [23.8%] drinkers) of 42 APA cases were well matched with the control group. In univariate analysis, BMI and VAT area were significantly higher in APA cases than those in matched controls; however, SAT area did not differ between them. The prevalence of diabetes mellitus was significantly higher in the APA group than those in the control group, whereas serum high-density lipoprotein (HDL) cholesterol and low-density lipoprotein cholesterol levels were lower in the APA group than those in the control group.

In multivariable conditional logistic regression analysis, the adjusted odds ratio (OR) (95% CI, *P* value) for APA for 1-SD increase in BMI (per 3.65 kg/m²) was 1.61 (1.13-2.30, 0.009) in model 1 (Table 2). In model 2, the OR for 1-SD increase in VAT area (per 59.40 cm²) was 1.88 (1.24-2.87, 0.003). In model 3, the OR for 1-SD increase in SAT area (per 62.03 cm²) was 1.23 (0.90-1.69, 0.192). In model 4, VAT area was significantly associated with APA (the adjusted OR [95% CI, *P* value] for 1-SD increase in VAT: 2.11 [1.23-3.62, 0.006]), but SAT area was not associated (the adjusted OR [95% CI, *P* value] for 1-SD increase in SAT: 0.87 [0.57-1.31, 0.495]). In model 5, residual VAT and SAT areas were not significantly associated with APA (the adjusted ORs [95% CI, *P* value] for each 1-SD increase in residual VAT (per 34.89 cm²) and SAT area (per 35.81 cm²): 1.18 [0.84-1.68, 0.344] and 0.71 [0.50-1.02, 0.067], respectively). Sensitivity analysis showed similar results to the primary analysis in terms of the point estimates (Supplementary Table 2) [30].

The AUC of model 2, including VAT area and other covariates, were significantly higher than that of model 3, including SAT area and other covariates, with a difference (95% CI, *P* value) of 0.10 (0.03-0.20, 0.011) (Table 2). Random forest showed that VAT area was the better predictor of APA than SAT area and BMI (Fig. 2).

There was evidence of interactions; obesity parameters with sex in association with APA (*P* for interactions 0.002 for BMI in model 1, 0.129 for VAT area in model 2, and 0.003 for SAT area in model 3). The association between obesity and APA was stronger in men than in women. Stratified analysis showed that the adjusted ORs (95% CI, *P* value) for

APA for each 1-SD increase were 4.62 (1.98-10.80, <0.001) for BMI (per 2.89 kg/m²) in model 1, 2.49 (1.38-4.49, 0.003) for VAT area (per 57.94 cm²) in model 2, and 2.68 (1.38-5.22, 0.004) for SAT area (per 54.52 cm²) in model 3 among men (Table 3). Among women, on the other hand, BMI, VAT, and SAT areas were not associated with APA from models 1 to 5 (Table 3). Sensitivity analysis showed similar results with *P* values for interactions 0.005 for BMI, 0.289 for VAT area, and 0.007 for SAT area (Supplementary Table 3) [30].

Random forest variable importance to predict APA showed that VAT area was more than 1.5 times as important as SAT area among men (Supplementary Figure 1) [30].

Comparisons of Patients With IHA and Controls

Age (51.8 \pm 8.9 years), sex (42 [61.8%] women), smoking (18 [26.5%] current smokers), and drinking status (17 [25.0%] drinkers) of 68 IHA cases were well matched with the control group (Table 1). In univariate analysis, BMI, VAT area, and SAT area were significantly higher among IHA cases than those among the matched controls. The prevalence of diabetes mellitus was significantly higher in the IHA group than those in the control group. IHA cases had higher serum triglyceride levels and lower HDL cholesterol levels than the controls.

In multivariable conditional logistic regression analysis, the adjusted OR (95% CI, *P* value) for IHA for 1-SD increase in BMI (per 3.88 kg/m²) was 3.09 (2.18-4.38, <0.001) in model 1 (Table 2). In model 2, the OR for 1-SD increase in VAT area (per 63.85 cm²) was 3.15 (2.14-4.63, <0.001). In model 3, the OR for 1-SD increase in SAT area (per 71.21 cm²) was 2.33 (1.71-3.18, <0.001). In model 4, VAT area was significantly associated with IHA (the adjusted OR [95% CI, *P* value] for 1-SD increase in VAT: 2.37 [1.46-3.86, <0.001]), but SAT area was not (the adjusted OR [95% CI, *P* value] for 1-SD increase in SAT: 1.42 [0.95-2.12, 0.086]). In model 5, only BMI was significantly associated with IHA, but not residuals of VAT and SAT areas. Sensitivity analysis showed similar results to the primary analysis in terms of the point estimate and significance (Supplementary Table 2) [30].

The AUC were not significantly different between models 2 and 3 (Table 2). Random forest variable importance to predict IHA showed that VAT area was more than 1.5 times as important as SAT area (Fig. 2).

There was no evidence of interactions; obesity parameters with sex in association with IHA (*P* for interactions 0.257 for BMI in model 1, 0.045 for VAT area in model 2, and 0.122 for SAT area in model 3). In stratified analysis, VAT area in model 4 and residual VAT area in model 5 were significantly associated with IHA, but not SAT area and residual SAT area among women (Table 3). Similarly, random forest variable importance to predict IHA showed that VAT area was a better predictor than SAT area among women (Supplementary Figure 1) [30].

Comparisons of Patients With APA and IHA

In univariate analysis, BMI, VAT, and SAT areas of IHA cases were higher than those of APA cases with *P* values 0.003, 0.020, and 0.001, respectively (Table 1). The VAT/SAT area ratio tended to be higher in APA cases than that of IHA cases but not significantly with a *P* value of 0.851. Serum sodium was higher and serum potassium was lower in APA cases than those in IHA cases with *P* values < 0.001 and < 0.001, respectively. The PAC and ARR with median (IQR) of 305.5

Table 1. Baseline characteristics of the patients with primary aldosteronism and matched controls

	APA (n = 42)	Control matched with APA (n = 168)	P value	IHA (n = 68)	Control matched with IHA (n = 272)	P value
Women, n (%)	22 (52.4)	88 (52.4)	1.000	42 (61.8)	168 (61.8)	1.000
Age, mean ± SD, y	50.9 ± 11.2	51.1 ± 10.8	0.934	51.8 ± 8.9	52.0 ± 8.8	0.897
Current smokers, n (%)	6 (14.3)	24 (14.3)	1.000	18 (26.5)	58 (21.3)	0.454
Alcohol drinking, n (%)	10 (23.8)	40 (23.8)	1.000	17 (25.0)	68 (25.0)	1.000
Body mass index, mean ± SD, kg/m ²	24.4 ± 4.3^a	22.8 ± 3.5	0.010	26.8 ± 4.2^a	22.7 ± 3.3	<0.001
Systolic blood pressure, mean ± SD, mm Hg	144.1 ± 15.2	117.1 ± 11.3	<0.001	142.0 ± 14.8	117.0 ± 12.1	<0.001
Diastolic blood pressure, mean ± SD, mm Hg	87.7 ± 8.8	72.6 ± 8.9	<0.001	88.1 ± 11.4	72.3 ± 8.9	<0.001
Fasting glucose, mean ± SD, mg/dL	106.1 ± 26.3 (n = 31)	98.5 ± 15.2	0.027	103.9 ± 19.1 (n = 57)	97.8 ± 16.3	0.013
Hemoglobin A1c, %, mean ± SD	5.6 ± 1.1 (n = 37)	5.6 ± 0.5	0.630	5.8 ± 0.7 (n = 62)	5.6 ± 0.5	0.002
Diabetes mellitus, n (%)	9 (29.0) (n = 31)	11 (6.5)	<0.001	11 (20.0) (n = 55)	13 (4.8)	<0.001
Triglyceride, median (IQR), mg/dL	109.0 (71.0-141.0) (n = 35)	84.5 (62.8-119.3)	0.017	125.0 (100.0-166.0) (n = 57)	84.5 (63.05-126.0)	<0.001
HDL cholesterol, mean ± SD, mg/dL	54.9 ± 15.3 (n = 34)	68.1 ± 18.5	<0.001	49.8 ± 13.7 (n = 57)	69.7 ± 18.7	<0.001
LDL cholesterol, mean ± SD, mg/dL	110.6 ± 30.5 (n = 33)	127.6 ± 31.8	0.005	117.2 ± 27.7 (n = 56)	126.8 ± 29.7	0.027
eGFR, mean ± SD, mL/min/1.73 m ²	82.6 ± 13.2	82.4 ± 10.8	0.930	82.9 ± 10.1	82.2 ± 9.0	0.573
Serum sodium, mean ± SD, mEq/L	144.0 ± 2.0^a	141.4 ± 1.8	<0.001	142.2 ± 1.5^a	141.8 ± 1.8	0.096
Serum potassium, mean ± SD, mEq/L	3.3 ± 0.6^a	4.1 ± 0.3	<0.001	4.0 ± 0.4^a	4.1 ± 0.3	<0.001
Serum uric acid, mean ± SD, mg/dL	5.1 ± 1.5	5.2 ± 1.4	0.566	5.4 ± 1.3	5.1 ± 1.4	0.156
Serum albumin, mean ± SD, mg/dL	4.3 ± 0.3	4.5 ± 0.2	<0.001	4.5 ± 0.4	4.5 ± 0.3	0.558
Plasma aldosterone, median (IQR), pg/mL	305.5 (167.5-480.8)^a	-	-	120.0 (95.6-158.0)^a	-	-
Plasma renin activity, median (IQR), ng/mL/h	0.2 (0.1-0.3)^a	-	-	0.2 (0.3-0.5)^a	-	-
ARR, median (IQR)	1435 (774-2411)^a	-	-	368 (241-600)^a	-	-
Serum cortisol in the morning, median (IQR), µg/dL	11.6 (7.1-14.6) (n = 39)	-	-	9.0 (7.1-11.7) (n = 61)	-	-
Antihypertensive medication, n (%)	5 (11.9)	4 (2.4)	0.021	8 (11.8)	9 (3.3)	0.011
Lipid lowering medication, n (%)	8 (19.0)	13 (7.7)	0.058	17 (25.0)	23 (8.5)	<0.001
Statin, n (%)	7 (16.7)	8 (4.8)	0.019	13 (19.1)	17 (6.2)	0.002
Potassium supplement, n (%)	25 (59.5)^a	0 (0.0)	<0.001	5 (7.4)^a	0 (0.0)	<0.001
Number of hypertensive medications, median (IQR)	1.0 (1.0-2.0)	-	-	1.0 (1.0-1.0)	-	-
Years to be hypertensive, median (IQR)	8.5 (3.0-16.0)^a	-	-	1.0 (1.0-4.0)^a	-	-
Medical history of CHD, n (%)	0 (0.0)	2 (1.2)	1.000	1 (1.5)	2 (0.7)	1.000
Medical history of stroke, n (%)	3 (7.1)	0 (0.0)	0.006	1 (1.5)	0 (0.0)	0.453
VAT areas, mean ± SD, cm ²	111.9 ± 69.4	86.1 ± 55.7	0.012	1404.5 ± 70.9	89.0 ± 56.9	<0.001
SAT areas, mean ± SD, cm ²	138.7 ± 68.5^a	125.2 ± 60.2	0.207	187.9 ± 75.8^a	125.2 ± 64.3	<0.001
VAT/SAT areas ratio, median (IQR)	0.73 (0.44-1.15)	0.62 (0.40-0.95)	0.097	0.68 (0.50-1.06)	0.62 (0.43-0.94)	0.052
Adrenal mass, n (%)	41 (97.6)^a	-	-	24 (35.3)^a	-	-

Data are expressed as means ± SD, median (IQR), or counts (percentages). For the difference of characteristics, skewed variables were tested using 2-sample Wilcoxon rank-sum (Mann-Whitney) test; normal variables were tested using 2-sample *t* test; categorical variables were tested using χ^2 test. Statistical significance was defined by a 2-sided *P* value < 0.017 according to Bonferroni correction from multiple comparison test. Significant values are displayed in bold. Abbreviations: ARR, plasma aldosterone to active renin ratio; CHD, coronary heart disease; eGFR, estimated glomerular filtration; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. ^aSignificant associations were found between APA vs IHA.

Table 2. The association between the parameters of obesity and disease status

		Odds ratio (95% CI)	P value	AUC (95% CI)	The difference of AUC	P value
APA vs matched control						
Model 1	BMI (kg/m ²)	1.61 (1.13-2.30)	0.009	–	–	–
Model 2	VAT area (cm ²)	1.88 (1.24-2.87)	0.003	0.69 (0.61-0.77)	0.10 (0.03, 0.20)	0.011
Model 3	SAT area (cm ²)	1.23 (0.90-1.69)	0.192	0.59 (0.49-0.68)	Reference	–
Model 4	VAT area (cm ²)	2.11 (1.23-3.62)	0.006	–	–	–
	SAT area (cm ²)	0.87 (0.57-1.31)	0.495			
Model 5	BMI (kg/m ²)	1.67 (1.15-2.42)	0.007	–	–	–
	Residual VAT area (cm ²)	1.18 (0.84-1.68)	0.344			
	Residual SAT area (cm ²)	0.71 (0.50-1.02)	0.067			
IHA vs matched control						
Model 1	BMI (kg/m ²)	3.09 (2.18-4.38)	<0.001	–	–	–
Model 2	VAT area (cm ²)	3.15 (2.14-4.63)	<0.001	0.78 (0.71-0.83)	-0.01 (-0.06, 0.04)	0.783
Model 3	SAT area (cm ²)	2.33 (1.71-3.18)	<0.001	0.78 (0.72-0.83)	Reference	–
Model 4	VAT area (cm ²)	2.37 (1.46-3.86)	<0.001	–	–	–
	SAT area (cm ²)	1.42 (0.95, 2.12)	0.086			
Model 5	BMI (kg/m ²)	3.09 (2.17-4.39)	<0.001	–	–	–
	Residual VAT area (cm ²)	1.19 (0.87-1.63)	0.286			
	Residual SAT area (cm ²)	0.94 (0.71-1.24)	0.645			
IHA vs APA						
Model 1	BMI (kg/m ²)	2.46 (1.48-4.41)	0.001	–	–	–
Model 2	VAT area (cm ²)	2.48 (1.46-4.55)	0.002	0.72 (0.62-0.81)	-0.01 (-0.10, 0.08)	0.886
Model 3	SAT area (cm ²)	2.40 (1.47-4.24)	0.001	0.73 (0.63-0.82)	Reference	–
Model 4	VAT area (cm ²)	1.69 (0.90-3.39)	0.116	–	–	–
	SAT area (cm ²)	1.83 (1.02-3.49)	0.051			
Model 5	BMI (kg/m ²)	2.47 (1.48-4.45)	0.001	–	–	–
	Residual VAT area (cm ²)	1.40 (0.88-2.27)	0.159			
	Residual SAT area (cm ²)	1.38 (0.88-2.26)	0.178			

All models are adjusted for sex, age, current smoker, and drinking habit. Adjusted odds ratio (95% CIs) associated with a 1-SD increase of each obesity parameter are shown. For APA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 3.65 kg/m²; VAT area, 59.40 cm²; SAT area, 62.03 cm²; residual VAT area, 34.89 cm²; and residual SAT area, 35.81 cm². For IHA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 3.88 kg/m²; VAT area, 63.85 cm²; SAT area, 71.21 cm²; residual VAT area, 34.98 cm²; and residual SAT area, 38.52 cm². For APA and IHA patients, the 1-SD increment of each obesity parameter is as follows: BMI, 4.27 kg/m²; VAT area, 71.78 cm²; SAT area, 76.60 cm²; residual VAT area, 42.07 cm²; and residual SAT area, 44.39 cm². Residuals of VAT and SAT areas were derived from Willett and Stampfer's residual approach and were uncorrelated with BMI. Statistical significance was defined by a 2-sided P value < 0.017 according to Bonferroni correction from multiple comparison test. Significant values are displayed in bold.

Abbreviations: APA, aldosterone-producing adenoma; AUC, the area under the receiver operating characteristic curves; BMI, body mass index; CI, confidence interval; IHA, idiopathic hyperaldosteronism; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

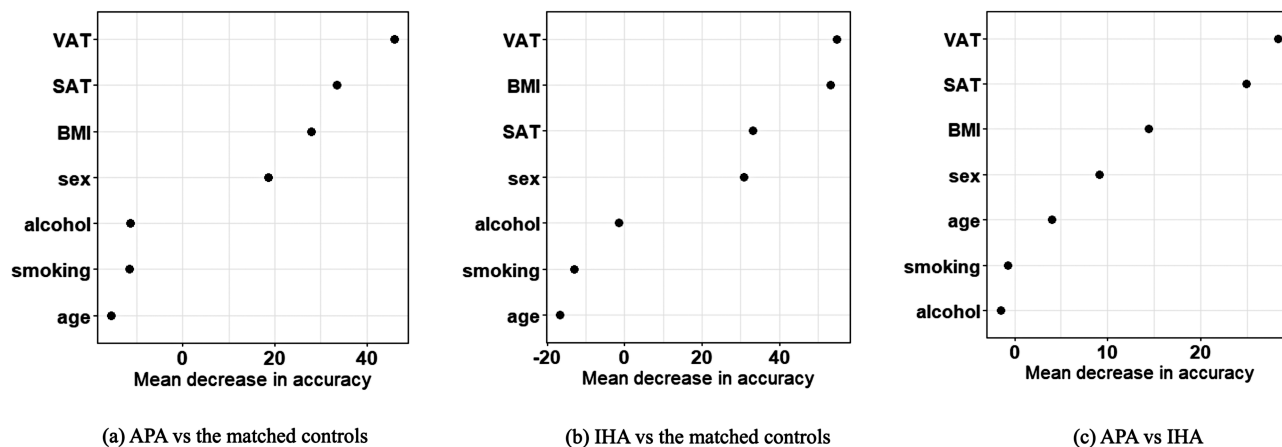


Figure 2. Random forest variable importance of patient characteristics to predict aldosterone-producing adenoma and idiopathic hyperaldosteronism. A larger mean decrease in accuracy indicates greater variable importance. We involved the following variables as potential predictive characteristics to include into the random forest: sex, age, current smoker, drinking habit, and obesity parameters (BMI, VAT area, and SAT area). APA, aldosterone-producing adenoma; BMI, body mass index; IHA, idiopathic hyperaldosteronism; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 3. The association between the parameters of obesity and disease status by sex

			Odds ratio (95% CI)	P value	AUC (95% CI)	The difference of AUC	P value	
APA vs matched control								
Men	Model 1	BMI (kg/m ²)	4.62 (1.98-10.80)	<0.001	–	–	–	
	Model 2	VAT area (cm ²)	2.49 (1.38-4.49)	0.003	0.77 (0.66-0.87)	0.01 (-0.11, 0.12)	0.895	
	Model 3	SAT area (cm ²)	2.68 (1.38-5.22)	0.004	0.76 (0.64-0.87)	Reference	–	
	Model 4	VAT area (cm ²)	1.82 (0.93-3.54)	0.080	–	–	–	
		SAT area (cm ²)	1.96 (0.99-3.88)	0.054	–	–	–	
	Model 5	BMI (kg/m ²)	4.79 (2.02-11.36)	<0.001	–	–	–	
		Residual VAT area (cm ²)	1.21 (0.69-2.11)	0.499	–	–	–	
		Residual SAT area (cm ²)	0.89 (0.51-1.57)	0.691	–	–	–	
	Women	Model 1	BMI (kg/m ²)	1.09 (0.69-1.72)	0.721	–	–	–
		Model 2	VAT area (cm ²)	1.19 (0.76-1.86)	0.233	0.59 (0.46-0.72)	0.02 (-0.17, 0.21)	0.825
Model 3		SAT area (cm ²)	0.78 (0.46-1.33)	0.370	0.57 (0.44-0.70)	Reference	–	
Model 4		VAT area (cm ²)	1.95 (0.96-4.00)	0.066	–	–	–	
		SAT area (cm ²)	0.49 (0.23-1.04)	0.065	–	–	–	
Model 5		BMI (kg/m ²)	1.11 (0.67-1.84)	0.693	–	–	–	
		Residual VAT area (cm ²)	1.30 (0.78-2.18)	0.310	–	–	–	
		Residual SAT area (cm ²)	0.52 (0.28-0.94)	0.030	–	–	–	
IHA vs matched control								
Men		Model 1	BMI (kg/m ²)	3.96 (2.03-7.73)	< 0.001	–	–	–
	Model 2	VAT area (cm ²)	2.39 (1.44-3.96)	< 0.001	0.75 (0.64, 0.84)	-0.10 (-0.19, -0.01)	0.037	
	Model 3	SAT area (cm ²)	3.36 (1.72-6.54)	< 0.001	0.85 (0.76, 0.92)	Reference	–	
	Model 4	VAT area (cm ²)	1.25 (0.63-2.49)	0.521	–	–	–	
		SAT area (cm ²)	2.83 (1.29-6.47)	0.014	–	–	–	
	Model 5	BMI (kg/m ²)	4.22 (2.13-8.35)	< 0.001	–	–	–	
		Residual VAT area (cm ²)	0.67 (0.37-1.22)	0.192	–	–	–	
		Residual SAT area (cm ²)	1.26 (0.75-2.09)	0.383	–	–	–	
	Women	Model 1	BMI (kg/m ²)	2.65 (1.77-3.96)	< 0.001	–	–	–
		Model 2	VAT area (cm ²)	3.13 (1.99-4.90)	< 0.001	0.80 (0.73-0.87)	0.05 (0.01, 0.10)	0.024
Model 3		SAT area (cm ²)	2.03 (1.42-2.90)	< 0.001	0.75 (0.68-0.82)	Reference	–	
Model 4		VAT area (cm ²)	3.57 (1.90-6.70)	< 0.001	–	–	–	
		SAT area (cm ²)	0.84 (0.48-1.48)	0.549	–	–	–	
Model 5		BMI (kg/m ²)	2.70 (1.75-4.17)	< 0.001	–	–	–	
		Residual VAT area (cm ²)	1.90 (1.24-2.92)	0.003	–	–	–	
		Residual SAT area (cm ²)	0.76 (0.52-1.12)	0.172	–	–	–	
IHA vs APA								
Men		Model 1	BMI (kg/m ²)	1.65 (0.86-3.56)	0.158	–	–	–
	Model 2	VAT area (cm ²)	1.51 (0.81-3.08)	0.220	0.59 (0.42, 0.78)	0.02 (-0.12, 0.19)	0.755	
	Model 3	SAT area (cm ²)	1.34 (0.68-2.95)	0.419	0.57 (0.40, 0.73)	Reference	–	
	Model 4	VAT area (cm ²)	1.47 (0.68-3.43)	0.344	–	–	–	
		SAT area (cm ²)	1.06 (0.45-2.63)	0.898	–	–	–	
	Model 5	BMI (kg/m ²)	1.61 (0.84-3.49)	0.178	–	–	–	
		Residual VAT area (cm ²)	1.07 (0.55-2.11)	0.834	–	–	–	
		Residual SAT area (cm ²)	0.84 (0.42-1.67)	0.602	–	–	–	

Table 3. Continued

			Odds ratio (95% CI)	P value	AUC (95% CI)	The difference of AUC	P value
Women	Model 1	BMI (kg/m ²)	2.93 (1.47-6.88)	0.006	–	–	–
	Model 2	VAT area (cm ²)	3.53 (1.70-8.75)	0.002	0.80 (0.68, 0.91)	-0.03 (-0.15, 0.01)	0.599
	Model 3	SAT area (cm ²)	4.23 (1.93-11.80)	0.001	0.83 (0.73, 0.93)	Reference	–
	Model 4	VAT area (cm ²)	2.00 (0.85-5.43)	0.139	–	–	–
		SAT area (cm ²)	2.91 (1.15-8.74)	0.035	–	–	–
	Model 5	BMI (kg/m ²)	3.46 (1.63-8.86)	0.004	–	–	–
		Residual VAT area (cm ²)	2.01 (0.97-4.65)	0.073	–	–	–
Residual SAT area (cm ²)		2.39 (1.16-5.63)	0.027	–	–	–	

All models are adjusted for age, current smoker, and drinking habit. Adjusted odds ratio (95% CIs) associated with a 1-SD increase of each obesity parameter are shown. For men among APA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 2.89 kg/m²; VAT area, 57.94 cm²; SAT area, 54.52 cm²; residual VAT area, 42.58 cm²; and residual SAT area, 32.83 cm². For women among APA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 3.93 kg/m²; VAT area, 41.22 cm²; SAT area, 68.35 cm²; residual VAT area, 26.24 cm²; and residual SAT area, 38.46 cm². For men among IHA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 3.75 kg/m²; VAT area, 70.87 cm²; SAT area, 66.81 cm²; residual VAT area, 43.66 cm²; and residual SAT area, 38.04 cm². For women among IHA patients and the matched controls, the 1-SD increment of each obesity parameter is as follows: BMI, 3.85 kg/m²; VAT area, 46.02 cm²; SAT area, 73.29 cm²; residual VAT area, 28.43 cm²; and residual SAT area, 38.91 cm². For men among APA and IHA patients, the 1-SD increment of each obesity parameter is as follows: BMI, 3.39 kg/m²; VAT area, 70.67 cm²; SAT area, 73.69 cm²; residual VAT area, 47.20 cm²; and residual SAT area, 43.73 cm². For women among APA and IHA patients, the 1-SD increment of each obesity parameter is as follows: BMI, 4.46 kg/m²; VAT area, 54.84 cm²; SAT area, 78.76 cm²; residual VAT area, 38.35 cm²; and residual SAT area, 45.21 cm². Residuals of VAT and SAT areas were derived from Willett and Stampfer's residual approach and were uncorrelated with BMI. Statistical significance was defined by a 2-sided *P* value < 0.017 according to Bonferroni correction from multiple comparison test. Significant values are displayed in bold. APA, aldosterone-producing adenoma; AUC, the area under the receiver operating characteristic curves; BMI, body mass index; CI, confidence interval; IHA, idiopathic hyperaldosteronism; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

(167.5-480.8) pg/mL and 1435 (774-2411) in APA cases were significantly higher than those with 120.0 (95.6-158.0) pg/mL and 368 (241-600) in IHA cases with *P* values < 0.001 and < 0.001, respectively. Serum cortisol levels tended to be higher in APA cases than that in IHA cases (*P* = 0.030). The adrenal mass was identified by CT in 41 (97.6%) APA cases, which was significantly higher than 24 (35.3%) IHA cases (*P* < 0.001).

In multivariable standard logistic regression analysis, the adjusted OR (95% CI, *P* value) for IHA for 1-SD increase in BMI (per 4.27 kg/m²) was 2.46 (1.48-4.41, 0.001) in model 1 (Table 2). In model 2, the OR for 1-SD increase in VAT area (per 71.78 cm²) was 2.48 (1.46-4.55, 0.002). In model 3, the OR for 1-SD increase in SAT area (per 76.60 cm²) was 2.40 (1.47-4.24, 0.001).

Although there was no evidence of interactions, obesity parameters with sex in association with PA subtype (*P* for interactions 0.552 for BMI in model 1, 0.048 for VAT area in model 2, and 0.087 for SAT area in model 3), obesity parameters were significantly higher in IHA cases than those in APA cases only in women, but not in men in stratified analysis (Table 3).

The Correlation Between Obesity Parameters and Adrenal Hormone Level

In APA cases, PAC and ARR had negative relationships with obesity parameters, but a significant association was found only between ARR and VAT area (*r* = -0.35, *P* = 0.023) (Supplementary Figure 2a) [30]. Serum cortisol levels did not have any significant association with obesity parameters. In stratified analyses by sex, ARR was negatively associated with VAT area among women (*r* = -0.52, *P* = 0.012) (Supplementary Figure 3a and 3b) [30].

In IHA cases, PAC and ARR were not associated with the parameters of obesity (Supplementary Figure 2b) [30]. Serum

cortisol levels were significantly negatively associated with obesity parameters. PAC was not significantly associated with obesity parameters in either men or women (Supplementary Figure 3c and 3d) [30].

Discussion

In this case control study, APA and IHA patients were more obese and had significantly higher VAT areas than their matched controls. There was an interaction between sex and obesity parameters in association with APA but not IHA. APA cases were more obese than the matched controls among men, but not among women. On the other hand, IHA cases were more obese than the controls among both men and women. These results helped to elucidate the mechanisms of a previous study's insight [16]: BMI was significantly higher in IHA patients than in APA among women, but not among men (Supplementary Figure 4) [30]. Moreover, we found that VAT areas had a closer association with APA and IHA than SAT areas.

Many previous studies found no significant association between PA and obesity [12-14], until Ohno et al showed that IHA but not APA cases had significant positive association with obesity [11]. We confirmed the observation that IHA cases were more obese than the normotensive controls. In contrast to Ohno et al, we found that APA cases were also more obese than the normotensive controls. We would speculate that our results differed from Ohno et al's because our studies used the controls with different clinical backgrounds. Previous studies, including Ohno et al's, used patients with essential hypertension who were more obese than the general population as controls [15]. However, we used normotensive healthy people as a control. Therefore, our controls were less obese than those of other studies. It is of note that the cases with IHA had significantly higher BMI than those with APA

even in the current study, corroborating the results of Ohno et al's study [11]. Taken together, it might be safe to conclude that patients with IHA are more obese than those with APA and that patients with APA are more obese than normotensive healthy people.

Sex might play an important role in the interaction between obesity and PA. Akasaka et al showed that BMI was significantly higher in IHA cases than in APA cases among women, but not among men [16]. Because their study subjects did not include non-PA cases, it was not clear whether patients of each sex were more obese than non-PA cases. To circumvent the limitation, we compared PA cases with healthy controls. The results showed that obesity parameters were significantly associated with APA among men, but not among women. On the other hand, among both sexes, obesity parameters were significantly associated with IHA. In short, male cases were obese whether they were APA or IHA, but female cases were obese in IHA, but not in APA. Similar to Akasaka et al's finding [16], we found a significant difference in BMI between IHA and APA in women, and found no difference in BMI between IHA and APA in men, probably because both IHA and APA cases were obese in men. In a clinical setting, these findings may be helpful to predict the subtype of PA among women; nonobese patients with PA may have a higher possibility of having APA, necessitating an adrenalectomy for often than obese patients. Among men, on the other hand, obese cases should be screened for PA more often than nonobese. Recent studies suggested the intriguing sex differences in the function of the mineralocorticoid receptor in the vascular endothelium [39]. The potential sex difference in the role of adiposity-specific mineralocorticoid receptor may contribute to the current result. Further studies are necessary to clarify mechanisms of the sex difference in the association between obesity and APA.

Obesity can be classified into 2 subtypes: visceral and subcutaneous adiposity. Shibayama et al reported a positive correlation of PAC with visceral fat area among IHA cases [23]. However, this study is limited to PA cases without a control group. To the best of our knowledge, the current study is the first to examine the association between VAT and PA status. Our study, which included normotensive healthy controls, showed that APA was significantly associated with VAT area, but not with SAT area. The results of the AUC difference and random forest also showed that VAT area was a better predictor of APA than SAT area. Similarly, IHA was significantly associated with VAT area, but not with SAT area in model 4. The results of random forest also showed that VAT area was a better predictor of IHA than SAT area. In short, compared with SAT area, VAT area had a closer association with both APA and IHA. Because visceral adiposity is known to be a risk factor for cardiovascular events in the general population [21, 22], the close association of PA with visceral adiposity may contribute to the established findings that patients with PA are at higher risk for developing cardiovascular events than patients without PA [4-7, 40]. The mechanisms leading to a closer association of PA with VAT than with SAT are not clear. Further studies are needed to clarify them.

Our study subjects included a control group matched for sex, age, current smoking, and drinking habit whose mean BMIs (SD) (23.6 kg/m² [2.8] for men and 22.5 kg/m² [3.6] for women) were almost the same as those among Japanese people between 40 and 69 years of age in 2012 (23.8 kg/m²

[3.2] for men and 22.5 kg/m² [3.6] for women) according to the National Health and Nutrition Survey [41]. However, the current study has several limitations. First, CT scan machines differed between PA cases and health checkup participants; therefore, precise comparison of the parameters such as VAT and SAT area may not be justified. Second, this was a cross-sectional case-control study. Therefore, it is impossible to determine a causal relationship. Third, our data did not include the information of menopausal status or serum estradiol levels, which might influence the associations between adipose tissue and PA. Fourth, multicollinearity between obesity parameters might bias the results. To minimize such weakness, however, we used random forest, a machine learning algorithm [24]. Because of the small sample size, our analysis models might be overfitted, including the random forest. The current results might be distorted by the potential selection bias. Obese patients might be more regularly screened for hypertension and PA than nonobese ones. As a result, the number of obese patients in the PA group may have been artificially inflated. Last, we could not perform CYP11B2 (aldosterone synthase) immunohistochemistry examination of adrenalectomy specimens for patients operated for unilateral PA as our study was mainly conducted before the H1STALDO (histopathology of primary aldosteronism) consensus was issued [42]. It could result in the measurement bias: the misdiagnosis as an aldosterone producing-adenoma or nodule rather than nonclassical unilateral subtype including multiple aldosterone-producing nodules or micronodules, or aldosterone-producing diffuse hyperplasia.

Conclusions

APA patients were more obese than normotensive controls in the case of men. IHA patients were more obese than normotensive controls whether they were men or women. IHA cases were more obese than APA cases among women, but not among men. VAT areas had closer associations with both APA and IHA than SAT areas. The present study may provide new insight on the association between PA and obesity, and may contribute to the prevention, the diagnosis, and treatment of PA.

Acknowledgments

We thank physicians and nurses in the division of Endocrinology and Metabolism in Jichi Medical University Hospital for their commitment and important contributions. We are indebted to the Cardiology Department and Radiology Department in the hospital for their contribution at performing adrenal vein sampling. We also deeply appreciate Jichi Medical University Health Care Center and Mr. Goma for performing health checkups.

Author Contributions

Study concept and design: Y.H., K.O., T.K., M.M., S.H., S.N., K.E., and S.I. Acquisition of data: N.S., H.M., and M.T. Analysis and interpretation of data: Y.H., K.O., T.K., M.T., T.S., H.M., K.K., and S.I. Drafting of the manuscript: Y.H., N.S., T.K., and S.I. Critical revision of the manuscript for important intellectual content: M.T., M.M., S.H., T.S., S.N., K.E., H.M., K.K., and S.I. Statistical analysis: Y.H. Study

supervision: S.I. Y.H. and N.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

S.I. has received personal fees or grants from MSD, Amgen, Astellas BioPharma, Eli Lilly Japan, Sanofi, Astellas Pharma, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Takeda Pharmaceutical, Ono Pharmaceutical, Shionogi, Teijin Pharma, and Kowa Pharmaceutical. The other authors state that they have no conflicts of interest.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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