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Relationship Between Visceral Fat and Plasma Aldosterone Concentration in Patients With Primary Aldosteronism

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Context: The involvement of visceral fat in aldosterone secretion has not been reported in patients with primary aldosteronism (PA). Patients with PA are complicated by metabolic syndrome more frequently than those without PA. An excess of visceral fat has been hypothesized to cause an elevation of aldosterone secretion in patients with PA.

Objectives: To clarify the role of visceral fat in the pathophysiology of PA, we investigated the correlation between plasma aldosterone concentration (PAC) and visceral fat parameters in patients with PA.

Design: This retrospective observational study comprised 131 patients diagnosed with PA between April 2007 and April 2017 at Sapporo City General Hospital. We divided participants into two PA subtypes, aldosterone-producing adenoma (APA; n = 47) and idiopathic hyperaldosteronism (IHA, n = 84), utilizing adrenal venous sampling. We analyzed the correlations of PAC with visceral fat percentage (VF%), visceral fat area (VFA), and subcutaneous fat area, by evaluating computed tomography studies in each subtype group.

Results: Patients with IHA showed a positive correlation of PAC with VF% ($r = 0.377$, $P < 0.001$) and VFA ($r = 0.443$, $P < 0.001$). The correlation was not evident in patients with APA.

Conclusions: This study revealed a relationship between visceral adipose tissue and aldosterone production only in patients with IHA.

Freeform/Key Words: hypertension, idiopathic hyperaldosteronism, obesity, primary aldosteronism, visceral adipose tissue

Since the 1960s, a number of studies have shown the association between obesity and essential hypertension [1]. Abdominal fat distribution has been well recognized as increasing the risk of health problems, namely, metabolic syndrome [2]. In particular, visceral adipose

Abbreviations: ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma; ARR, aldosterone renin ratio; AVS, adrenal venous sampling; BMI, body mass index; CT, computed tomography; DST, dexamethasone suppression test; IHA, idiopathic hyperaldosteronism; IVC, inferior vena cava; LI, lateralized index; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SCFA, subcutaneous adipose area; VAT, visceral adipose tissue; VFA, visceral fat area; VF%, visceral fat percentage.

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tissue (VAT) is independently correlated with hypertension, insulin resistance, dyslipidemia, and, ultimately, coronary heart disease [3].

Primary aldosteronism (PA) is one of the most common forms of secondary hypertension, with prevalence of up to 10% of all patients with hypertension [4, 5]. Metabolic syndrome is more frequent in patients with PA than in patients with essential hypertension, with equivalent body mass index (BMI) and blood pressure [6]. Monticone *et al.* [7] reported that compared with patients with essential hypertension, patients with PA had an increased risk of stroke, coronary artery disease, atrial fibrillation, diabetes, and metabolic syndrome. Among patients with PA, BMI is significantly higher in patients with nonlateralized PA than in those with lateralized PA [8].

We established our database of patients with PA, with quantitative determination of VAT using computed tomography (CT). We hypothesized that VAT is involved in the elevation of aldosterone secretion in PA, based on a previous report suggesting a positive correlation between plasma aldosterone concentration (PAC) and visceral fat area (VFA) in patients without PA [9]. Therefore, we explored the correlation between precise VAT volume and PAC in patients with PA. Because the pathophysiology of hypertension in PA is fundamentally different between aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA), we further investigated the correlation of VAT volume to PAC, either in APA or in IHA, which were discriminated using adrenal venous sampling (AVS).

1. Patients and Methods

A. Patients

This was a retrospective observational study comprising 131 patients. Patients diagnosed with PA between April 2007 and April 2017 at Sapporo City General Hospital were included in this study.

The diagnostic procedure for PA at our institute is performed with reference to the guidelines of both the Japan Endocrine Society [10] and the Japan Society of Hypertension [11]. Briefly, the ratio of the PAC (pg/mL) to the plasma renin activity (PRA) (ng/mL/h) >200 is used for screening after a change from antihypertensive drugs to calcium channel blockers and/or α-blockers, where applicable. The diagnosis of PA was established with at least one positive result in confirmatory testing including the captopril challenge test, the upright-furosemide loading test, and the saline loading test. We excluded patients with suspected autonomous cortisol secretion, defined as serum cortisol levels ≥3 μg/dL after a 1-mg dexamethasone suppression test (DST) [12].

B. AVS

Prior to and at 30 minutes after adrenocorticotropic hormone (ACTH) administration, blood samples were collected via AVS from both adrenal veins and from the inferior vena cava (IVC) at a point distal to the renal vein. As the protocol for ACTH administration, we used a bolus injection of 250 μg of cosyntropin. Sampling of the left and right adrenal veins was performed simultaneously. Catheterization was considered to be successful if the selectivity index (the ratio of cortisol concentration between the adrenal vein and the IVC) was more than 5 or the serum cortisol concentration was more than 200 μg/dL in the adrenal vein after ACTH administration [13]. We excluded the patients with unsuccessful AVS.

To evaluate the laterality of aldosterone secretion using AVS, we divided patients into two groups, patients with unilateral hyperaldosteronism and those with bilateral hyperaldosteronism. Unilateral hyperaldosteronism was defined if the lateralized index (LI; the ratio of aldosterone to cortisol concentration between the dominant and nondominant adrenal glands) was more than 4 after ACTH administration [14–16]. Bilateral hyperaldosteronism was defined as LI less than 2 after ACTH administration [17]. To exclude

patients with a possible ambiguous diagnosis using AVS, we did not enroll those patients with LI 2 to 4 after ACTH administration in this study.

C. Subtype of PA

Patients with PA were subtyped into two groups, APA and IHA, according to AVS results. APA was defined as a case in which both findings of unilateral lesion with AVS and adrenocortical adenoma with pathology were observed. IHA was defined as a case in which bilateral hyperaldosteronism was observed in AVS.

D. Scanning for Intra-Abdominal Fat Volume Using Multidetector CT

Participants were examined in a supine position with both arms stretched above the head using a Toshiba Aquillio ONE CT scanner (Tokyo, Japan). We obtained a 64-slice multidetector CT scan with a tube voltage of 120 kV, automatically controlled tube current, and pitch factor of 0.828, starting at the upper edge of the liver and continuing to the pelvis. After the administration of 540 mgI/kg/s contrast agent (Iopamidol for patients with body weight $\geq$55 kg, Iohexol for patients with body weight $<$55 kg), scanning was performed at 30, 90, and 180 seconds after confirming that the CT value at the aorta was more than 230 Hounsfield units. The tube current was automatically controlled with automatic exposure control. All patients underwent thin-slice (2-mm-thick) CT. Adrenal tumors detected with CT were defined as tumors larger than 10 mm in diameter. We evaluated visceral fat percentage (VF%), VFA, subcutaneous adipose area (SCFA), and waist circumference using Synapse Vincent version 4.4 (Tokyo, Japan).

Adipose tissue was automatically detected with software on the basis of attenuation number, using a window level of –50 to –270 Hounsfield units. The intra-abdominal visceral fat volume was measured by drawing a line within the muscle wall surrounding the abdominal cavity, starting at the upper edge of the liver and continuing to the pelvis. VF% was calculated by dividing the intra-abdominal visceral fat volume by the total abdominal volume. VFA, SCFA, and the waist circumference were determined at the umbilical level.

E. Analysis

In this study, we used two different parameters to represent the visceral fat volume, namely, VF% and VFA using CT. We analyzed the correlation of PAC measured in the early morning at the hospital, with the patient in recumbent resting position with VF%, VFA, SCFA, and waist circumference in patients with each subtype. In addition, we analyzed the correlation of PAC with the baseline characteristics, age, body height, body weight, BMI, PRA, aldosterone renin ratio (ARR), and serum cortisol levels after a 1-mg DST.

We estimated the postoperative clinical and biochemical outcomes of patients who underwent unilateral adrenalectomy, referring to the Primary Aldosteronism Surgery Outcome study over either a 6- or 12-month follow-up [18].

F. Assay Methods

PAC was determined using radioimmunoassay (SPAC-S Aldosterone Kits; Fuji Rebio, Co., LTD, Tokyo, Japan). The reference range of PAC in the supine position was 30 to 159 pg/mL, according to the manufacturer's instructions. PRA was measured using radioimmunoassay, with the reference range in the supine position 0.3 to 2.9 ng/mL/h (PRA Radioimmunoassay Kits; Fuji Rebio, Co., LTD).

G. Statistics

The data were analyzed and compared using Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). Continuous variables were expressed as either mean $\pm$ SD

or median and interquartile range. Correlation was analyzed using the Spearman rank correlation coefficient. Continuous variables were analyzed by *t* test or the Mann-Whitney *U* test, as appropriate. Comparison of the frequency among two groups was estimated by either the χ^2 test or the Fisher exact test, as appropriate. Statistical significance was achieved when the *P* value was <0.05.

2. Results

A flowchart of this study is shown in Fig. 1. A total of 292 patients with PA were enrolled, and 184 patients underwent AVS. Fifty-five patients were diagnosed with unilateral hyperaldosteronism using AVS. Forty-seven patients underwent unilateral adrenalectomy and were diagnosed with adrenocortical adenoma. Ninety-one patients were diagnosed with bilateral hyperaldosteronism using AVS. Of these patients, we excluded those in whom we could not exclude the possibility of having unilateral hyperaldosteronism regardless of whether they were diagnosed with bilateral hyperaldosteronism according to AVS. We excluded patients with apparent bilateral aldosterone suppression, defined as lower aldosterone/cortisol ratios in the bilateral adrenal veins than that in the IVC [19, 20]. We also excluded patients diagnosed with unilateral hyperaldosteronism using a repeat AVS or segmental AVS [21]. Finally, 47 patients (25 males, 22 females) with

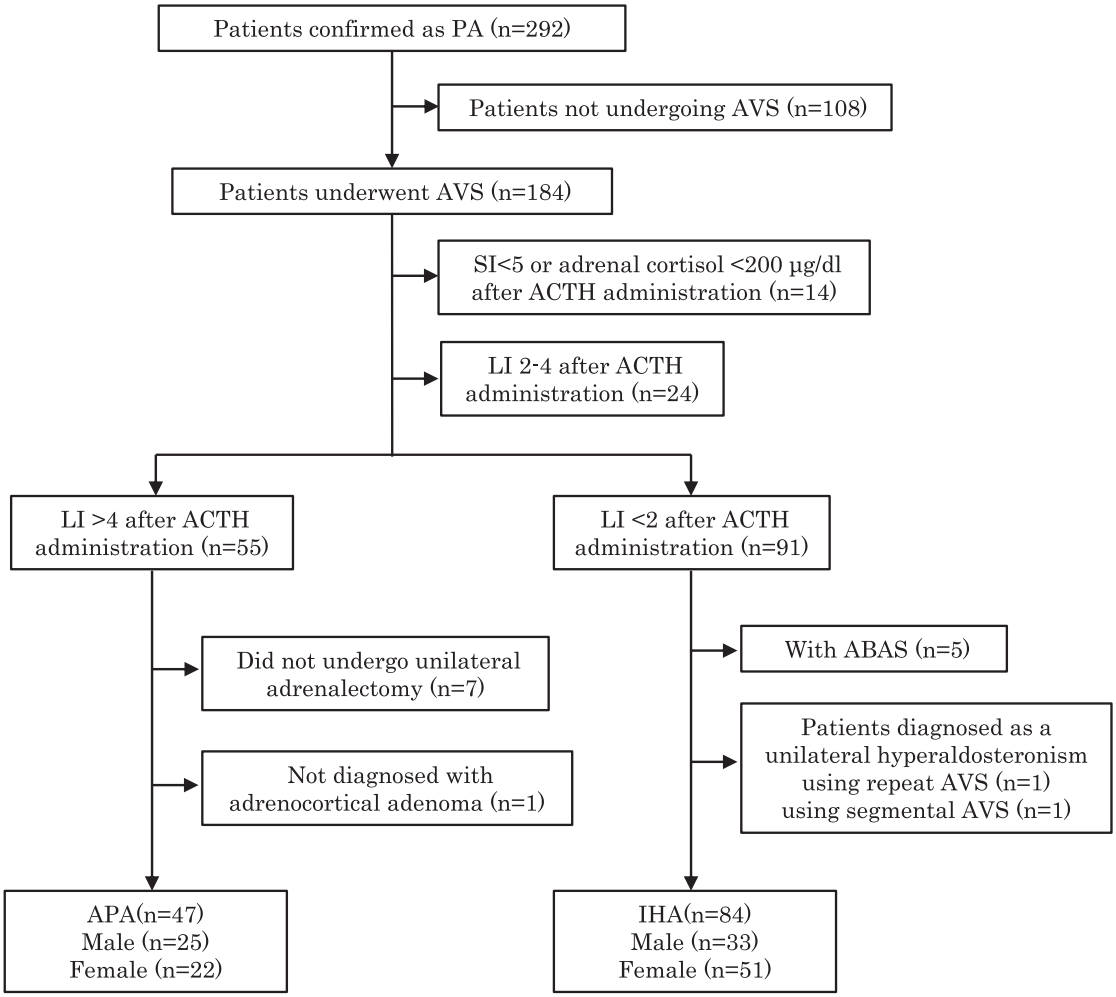

Figure 1. Flowchart of patients with each PA subtype. SI, selectivity index.

APA and 84 patients (33 males, 51 females) with IHA were eligible for inclusion in this study.

The characteristics of patients with APA and IHA are summarized in Table 1. The frequency of female participants was not different between these two subtypes ($P = 0.18$); BMI was also not different between the subtypes. Duration of hypertension was significantly longer in patients with APA ($P = 0.01$), and PRA was significantly lower in patients with APA than those with IHA. PAC and ARR were significantly higher in patients with APA than in those with IHA ($P < 0.001$, $P < 0.001$, respectively). Serum potassium levels were significantly lower in patients with APA than in those with IHA ($P < 0.001$), and the percentages of potassium supplement were significantly higher in patients with APA than in those with IHA ($P < 0.001$). There were significantly more patients with APA who had adrenal tumors detected with CT than patients with IHA ($P < 0.001$).

A 1-mg DST was performed in 28 (59.6%) patients with APA and 62 (73.8%) with IHA. Four (14.3%) patients with APA and 6 (9.7%) with IHA displayed serum cortisol levels between 1.8 μg/dL and 3.0 μg/dL. Patients who did not undergo a 1-mg DST had serum cortisol levels measured at 23:00, and these values did not exceed 5 μg/dL.

A comparison of the adipose parameters and waist circumference between APA and IHA is shown in Table 2. VF% was significantly higher in patients with IHA than in those with APA (APA vs IHA: 22.9% ± 10.8% vs 27.6% ± 10.2%; $P = 0.02$). Patients with IHA showed a tendency to have higher VFA, but this was not significantly different between the two subtypes (APA vs IHA: 90.6 ± 54.1 cm^2 vs 97.0 ± 7.9 cm^2; $P = 0.52$). SCFA and waist circumference were not different between subtypes (Table 2).

When we categorized patients in each subtype according to sex, both male and female patients with IHA showed a tendency toward higher VF% and VFA than those with APA. Only in female participants, VF% was significantly higher in patients with IHA than in those with APA (APA vs IHA: 16.9% ± 1.9% vs 25.1% ± 1.4%; $P = 0.001$) (Fig. 2).

The correlations between PAC and each factor in patients with IHA are shown in Fig. 3. Positive correlations of PAC were found with VF% ($r = 0.377$, $P < 0.001$) (Fig. 3A), VFA ($r = 0.443$, $P < 0.001$) (Fig. 3B), BMI ($r = 0.386$, $P < 0.001$) (Fig. 3D), and waist circumference ($r = 0.354$, $P < 0.001$) (Fig. 3E). These correlations remained when we categorized patients with IHA by sex (data not shown). In contrast, patients with IHA did not show a significant correlation between PAC and SCFA ($r = 0.151$, $P = 0.170$) (Fig. 3C). No correlation was found between PAC and VF% ($r = –0.073$, $P = 0.629$), VFA ($r = 0.018$, $P = 0.904$), BMI ($r = 0.068$, $P = 0.648$), waist circumference ($r = 0.032$, $P = 0.831$), or SCFA ($r = –0.046$, $P = 0.759$) in patients

Table 1. Baseline Characteristics of the Patients With APA and IHA

	APA (n = 47)	IHA (n = 84)	*P* Value
Age (y)	51.5 ± 12.6	51.1 ± 11.3	0.85
Sex (male: female) (%)	25 (53%): 22 (47%)	33 (39%): 51 (61%)	0.18
Body height (cm)	162.6 ± 9.2	162.1 ± 9.2	0.79
Body weight (kg)	66.9 [55.6–75.1]	64.2 [57.0–72.8]	0.75
BMI	25.1 ± 4.0	25.0 ± 4.0	0.87
Systolic blood pressure (mm Hg)	138.0 [130.0–149.5]	139.0 [126.0–144.0]	0.40
Diastolic blood pressure (mm Hg)	79.5 [70.0–84.8]	82.0 [73.5–90.0]	0.11
Duration of hypertension (y)	7.0 [3.0–10.0]	3.0 [0.7–6.0]	0.01
Number of antihypertensive drugs	2.0 [1.0–2.0]	1.0 [0–2.0]	<0.001
PRA (ng/mL/h)	0.2 [0.1–0.3]	0.3 [0.2–0.5]	<0.01
PAC (pg/mL)	333 [228–459]	140 [115–170]	<0.001
ARR	1720 [1072–2640]	409 [285–858]	<0.001
Serum cortisol after 1-mg DST (μg/dL)	1.2 [0.9–1.5]	0.8 [0.6–1.2]	<0.01
Serum potassium level (mEq/L)	3.2 [2.8–3.6]	4.0 [3.8–4.1]	<0.001
Potassium supplement (%)	26 (55.3%)	4 (4.8%)	<0.001
Adrenal tumor (%)	44 (93.6%)	15 (17.9%)	<0.001

Data are expressed as either mean ± SD, median [interquartile range], or number (percentages).

Table 2. Comparison of Adipose Evaluation and Waist Circumference Between APA and IHA

	APA (n = 47)	IHA (n = 84)	*P* Value
VF% (%)	22.9 ± 10.8	27.6 ± 10.2	0.02
VFA (cm^2)	90.6 ± 54.1	97.0 ± 7.9	0.52
Subcutaneous fat area (cm^2)	141.1 ± 69.7	153.4 ± 7.3	0.32
Waist circumference (cm)	84.7 ± 10.9	85.2 ± 1.0	0.81

Data are expressed as mean ± SD. VF% was calculated by dividing intra-abdominal visceral fat volume by total abdominal volume. VFA, subcutaneous fat area, and waist circumference were determined at the umbilical level.

with APA. VF% was positively correlated with VFA ($r = 0.909$, $P < 0.001$) regardless of the subtype group, or the sex.

Postoperative outcomes could be evaluated in 42 of the 47 patients (89.4%) who underwent a unilateral adrenalectomy. Rates of complete, partial, and absent clinical success were 33.3% (14 patients), 40.5% (17 patients), and 26.2% (11 patients), respectively. In terms of biochemical success, complete, partial, and absent proportions were 83.3% (35 patients), 9.5% (4 patients), and 7.1% (3 patients), respectively.

3. Discussion

To the best of our knowledge, this is the first study to show a positive correlation of PAC with VF% and VFA, precisely evaluated by CT scanning in patients with PA. Furthermore, we examined these correlations by dividing patients with PA into two subtypes, APA and IHA, in accordance with AVS results.

In previous studies among non-PA populations, a correlation between aldosterone secretion and obesity or VAT was proven. PAC was found to be significantly higher in both obese hypertensive and obese normotensive patients than in lean normotensive patients [22]. Another study found that aldosterone levels among obese participants in the absence of PA were reduced after weight loss [23]. PAC has also been shown to be correlated with waist circumference in non-PA patients [24]. Rossi *et al.* [25] reported that BMI was independently correlated with PAC in obese participants with primary hypertension; however, the correlation was not evident in patients with PA, even after analyzing these patients independently according to APA and IHA groups. Goodfriend *et al.* [9] reported a positive correlation between PAC and VFA in women with obesity without PA and in those with essential hypertension. Tirosh *et al.* [26] reported a positive quadratic (U-shaped) correlation between

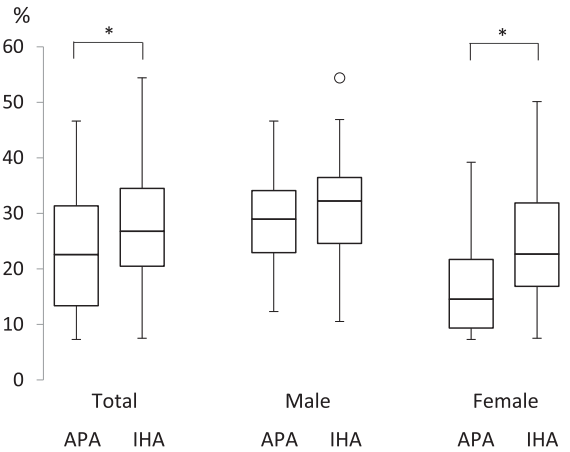

Figure 2. Comparison of VF% between APA and IHA for each sex. A comparison of VF% between patients with APA and IHA for each sex were presented. *$P < 0.05$.

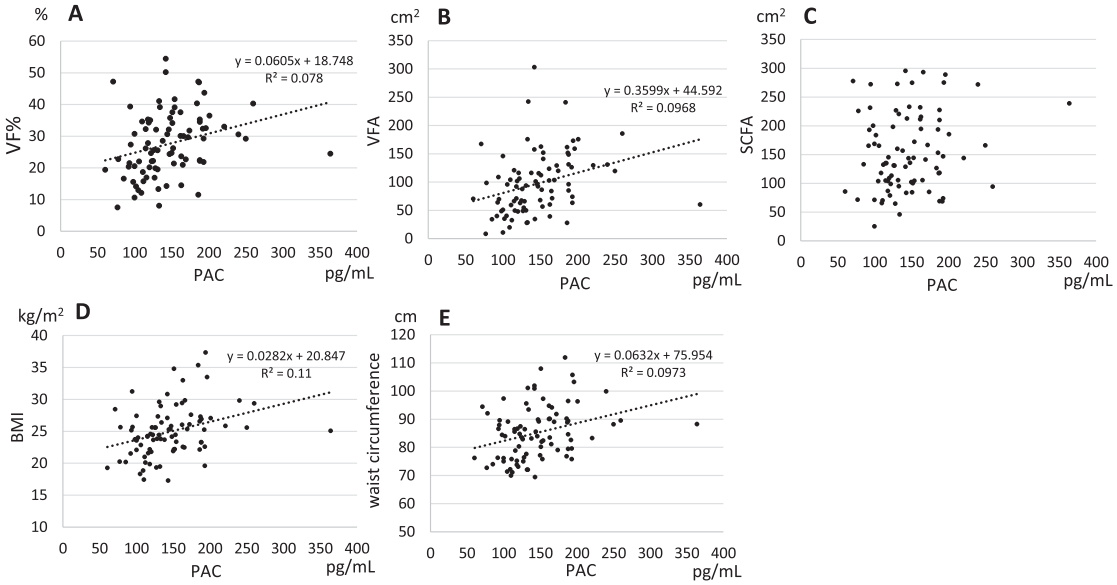

Figure 3. Correlation between PAC and each factor in patients with IHA. Correlation of PAC with (A) VF%, (B) VFA, (C) SCFA, (D) BMI, and (E) waist circumference in patients with IHA.

PAC and BMI, not only in non-PA patients, but also in those with PA. Considering those reports, the relationship has remained unclear between PAC and BMI, waist circumference, and visceral fat in patients with PA.

The existence of reciprocal cross-talk between the adipose organ and adrenal glands has been suggested [27]. Activation of mineralocorticoid receptor induces the differentiation of preadipocytes to mature adipocytes [28] as well as the expression of proinflammatory genes, such as tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant-1 [29]. In contrast, VAT is regarded as a potent mineralocorticoid-releasing factor [30]. A study showed leptin-regulated CYP11B2 expression and aldosterone release at the level of the adrenal zone glomerulosa cells via a calcium-dependent mechanism in mice [31]. Another study demonstrated expression of specific mRNAs of adiponectin receptors in normal human adrenal cortices. Adiponectin can modulate aldosterone secretion by acting on adiponectin receptor subtypes in the adrenal cortex [32]. The other study suggested that Complement-C1q tumor necrosis factor-related protein 1 was expressed in the zona glomerulosa of the adrenal cortex, stimulating aldosterone production through induction of CYP11B2 gene expression [33].

In this study, BMI and waist circumference were not different between patients with APA and those with IHA, although patients with APA had higher PAC. Furthermore, VF% was significantly higher in patients with IHA. These findings suggest that the effect of aldosterone on the increase of visceral fat in patients with PA was not significant. In contrast, a significant positive correlation was observed between PAC and VF% and VFA only in patients with IHA. Therefore, this suggests that the relationship between adipose tissue and aldosterone production was different between these two subtypes, and that visceral fat played a more important role on aldosterone production in patients with IHA, compared with patients with APA.

The strength of this study design was that VAT was directly evaluated using CT scanning, leading to more convincing results in comparison with studies using body weight, BMI, waist-to-hip ratio, or waist circumference for the evaluation. Furthermore, VAT was evaluated using two parameters, VF% and VFA.

The limitations of this study are as follows. Because this is a retrospective cohort study at a single center, we could not match the baseline profile in each subtype, including number of patients and sex ratio. In this study, the frequency of female participants was relatively

higher in patients with IHA than in those with APA, although this was not statistically significant. With the limited number of patients enrolled in our study, the sex distribution was different between patients with APA and those with IHA. We could not clarify the difference in fat distribution or the influence of the VAT on aldosterone production according to sex. Because patients with IHA rarely underwent unilateral adrenalectomy, we could not completely exclude the possibility of including patients with micro-APA or APA in the IHA group. In addition, because we could not perform 1-mg DST for all patients in this study, we could not completely exclude the possibility of including patients with autonomous cortisol secretion.

4. Conclusion

A positive correlation between aldosterone secretion and visceral fat was found in our patients with IHA. This study demonstrated a relationship between VAT and aldosterone production only in patients with IHA but not in those with APA. Patients with IHA would have better outcomes if they reduced visceral fat by intensive diet control. Our findings provide evidence for better management of PA in daily clinical practice.

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