ORIGINAL ARTICLE

Different pathogenesis of glucose intolerance in two subtypes of primary aldosteronism: Aldosterone-producing adenoma and idiopathic hyperaldosteronism

Mikiko Okazaki-Hada(iD), Ayako Moriya, Mototsugu Nagao*(iD), Shinichi Oikawa, Izumi Fukuda(iD), Hitoshi Sugihara

Department of Endocrinology, Diabetes and Metabolism, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

ABSTRACT

Aims/Introduction: An increased risk of diabetes mellitus has been reported in primary aldosteronism, but the pathogenesis of glucose intolerance between the primary aldosteronism subtypes remains unclear. This study aimed to evaluate glucose metabolism in oral glucose tolerance test between aldosterone-producing adenoma and idiopathic hyperaldosteronism, and characterize patients with improved glucose intolerance after primary aldosteronism treatment.

Materials and Methods: Oral glucose tolerance test was carried out in 116 patients who were diagnosed with primary aldosteronism and received adrenal venous sampling for subtyping. Oral glucose tolerance test was re-evaluated after starting the treatment of primary aldosteronism for those who had glucose intolerance before the treatment.

Results: A total of 46.4% and 52.3% of patients with aldosterone-producing adenoma and idiopathic hyperaldosteronism, respectively, were diagnosed with impaired glucose tolerance or diabetes. The insulinogenic index was significantly lower in aldosterone-producing adenoma than in idiopathic hyperaldosteronism ($P = 0.045$), whereas the Matsuda insulin sensitivity index was significantly higher in aldosterone-producing adenoma than in idiopathic hyperaldosteronism ($P = 0.022$). After the treatment of primary aldosteronism, glucose intolerance was improved in 66.6% and 45.8% of aldosterone-producing adenoma and idiopathic hyperaldosteronism, respectively. The presence of obesity and central obesity were significantly lower in patients who improved glucose intolerance after the treatment of primary aldosteronism as compared with those not improved ($P = 0.013$ and $P = 0.033$, respectively).

Conclusions: Insulin secretion impairment and insulin resistance play pathogenic roles for glucose intolerance in aldosterone-producing adenoma and idiopathic hyperaldosteronism, respectively. In addition, primary aldosteronism treatments can ameliorate glucose intolerance more effectively in patients without obesity and/or central obesity.

INTRODUCTION

Primary aldosteronism (PA) is the most common cause of secondary hypertension. Hyperaldosteronism is associated with increased risks of cardiovascular events and renal damage through blood pressure-dependent and blood pressure-independent mechanisms[1–4]. In addition, hyperaldosteronism causes abnormalities of glucose metabolism, and PA is regarded as an endocrine cause of diabetes mellitus[5]. Hyperaldosteronism has been considered to dysregulate glucose homeostasis in multifactorial ways. For instance, hypokalemia induced by hyperaldosteronism impairs insulin secretion and decreases insulin sensitivity[6,7]. Furthermore, aldosterone itself causes β-cell dysfunction and induces insulin resistance[8]. The major subtypes of PA include unilateral aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA) caused by bilateral

adrenal hyperplasia. These two subtypes account for >95% of all PA cases[9]. APA is caused by the autonomous overproduction of aldosterone by an adrenal adenoma. On the contrary, the cause of IHA is not fully elucidated. A recent report by Ohno *et al.*[10] suggested that obesity-related factors might account for the pathogenesis of IHA by analyzing the characteristics of 516 patients with APA and 1,015 patients with IHA. APA and IHA, therefore, have different pathogenesis and characteristics.

The difference in the pathogenesis of impaired glucose metabolism between APA and IHA is still unclear. Previous studies have shown controversial results regarding the amelioration of glucose metabolism after the treatment of PA. Catena *et al.*[11] reported that treatments of PA, including surgery or administration of aldosterone antagonists, significantly improve insulin resistance. Furthermore, Tsurutani *et al.*[6] reported that insulin secretion increased after adrenalectomy for APA, whereas Strauch *et al.*[12] reported that the treatment of PA did not improve glucose tolerance.

In the present study, we carried out the 75-g oral glucose tolerance test (OGTT) in the two subtypes of PA (APA and IHA) to elucidate the differences of glucose metabolism between the two subtypes. Furthermore, to confirm whether the treatment of PA improves glucose metabolism or not, we carried out OGTT again after the treatment of PA; that is, adrenalectomy or administration of mineralocorticoid receptor antagonists, for patients with impaired glucose tolerance (IGT) or diabetes in OGTT before the treatment. Finally, we analyzed the characteristics of patients with improved glucose intolerance after the treatment of PA.

METHODS

Participants

Patients who were admitted to Nippon Medical School Hospital (Tokyo, Japan) for adrenal venous sampling were enrolled in the present study ($n = 116$, 45 men and 71 women). All the patients were diagnosed with PA by the following confirmatory tests: the captopril challenge test, furosemide upright test and saline infusion test. Patients with bilateral APA, patients who were diagnosed with overt diabetes and Cushing's syndrome, and patients who were pregnant or currently taking steroids were excluded from the analysis. Patients with subclinical Cushing's syndrome according to the Japan Endocrine Society criteria[13] were also excluded. The study protocol was approved by the Nippon Medical School Ethical Committee (No. 28-07-611), and carried out in accordance with the principles of the Declaration of Helsinki.

Anthropometric measurements

Body mass index (kg/m^2) was calculated by the height and bodyweight at admission. Waist circumference was measured at the umbilical level. Obesity was defined as body mass index ≥ 25 kg/m^2 according to the guidelines for the management of obesity disease 2016 in Japan[14]. As an essential component of

metabolic syndrome[15], central obesity was defined as waist circumference ≥ 85 cm and ≥ 90 cm for men and women, respectively, based on the Japanese criteria[14].

Diagnosis of primary aldosteronism

PA was diagnosed according to the guidelines from the Japan Endocrine Society and the Japan Society of Hypertension[16,17]. Initially, antihypertensive drugs that influence the plasma aldosterone concentration (PAC) and plasma renin activity (PRA); for example, the aldosterone receptor blocker, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers, were discontinued and adjusted to calcium channel blockers or α-blockers before the examination. Subsequently, PA was screened when the aldosterone-to-renin ratio (ARR = PAC [pg/mL] / PRA [ng/mL/h]) was >200. The PAC and PRA were measured by radioimmunoassay (Fujirebio Inc., Tokyo, Japan). Next, the two or three aforementioned confirmatory tests were carried out, and the diagnosis of PA was confirmed when the result of at least one confirmatory test was positive. All the confirmatory tests were carried out in the morning after overnight fasting. Furthermore, when the patient's serum potassium concentration was ≤ 3.5 mEq/L, the patient received oral supplementation of potassium before undergoing the confirmatory tests.

Adrenal venous sampling

The subtype of PA was determined by adrenal venous sampling. Adrenal venous sampling was carried out by expert radiologists according to the methodologies described in the guidelines of the Japan Endocrine Society[16]. Adrenal vein cannulation was confirmed if the serum cortisol concentration was ≥ 200 µg/dL. When the serum aldosterone concentration in the adrenal vein was $\geq 14,000$ pg/mL, aldosterone hypersecretion of the adrenal gland was confirmed. The aldosterone-to-cortisol ratio was subsequently calculated in the right and left adrenal veins. The lateralized ratio was calculated by dividing the aldosterone-to-cortisol ratio of the higher side by that of the lower side. The contralateral ratio was calculated by dividing the aldosterone-to-cortisol ratio of the lower side by that of the inferior vena cava. The unilateral PA subtype (APA) was confirmed if the lateralized ratio and contralateral ratio were >4 and <1, respectively. Otherwise, the bilateral PA subtype (IHA) was confirmed[18]. All of these assessments were carried out after adrenocorticotropic hormone stimulation.

OGTT

All of the patients in the present study underwent 75-g OGTT before starting the treatment of PA. Plasma glucose (PG) and immunoreactive insulin (IRI) concentrations were measured before (0 min), and at 30, 60 and 120 min after glucose loading. According to the diagnostic criteria for diabetes from the American Diabetes Association and Japan Diabetes Society[19,20], patients were categorized into three groups. The patients whose PGs were <100 mg/dL at 0 min and <140 mg/dL at 120 min

were categorized into the normal glucose tolerance group (NGT), 140–199 mg/dL at 120 min into the IGT group, ≥126 mg/dL at 0 min or ≥200 mg/dL at 120 min into the diabetes group. To assess the insulin secretion, we calculated the homeostasis model assessment for β-cell function (HOMA-β)[21] and insulinogenic index[22]. To evaluate the insulin sensitivity, we used the homeostasis model assessment-insulin resistance (HOMA-IR)[21] and the Matsuda insulin sensitivity index[23]. The detailed equations of each index are as follows: HOMA-β = IRI at 0 min × 360 / (PG at 0 min − 63), insulinogenic index = (IRI at 30 min − IRI at 0 min) / (PG at 30 min − PG at 0 min), HOMA-IR = IRI at 0 min × PG at 0 min / 405 and Matsuda index = 10,000 / (PG at 0 min × IRI at 0 min × mean PG × mean IRI)$^{0.5}$. A portion of the patients who were classified into the IGT or diabetes group (3/13 patients in APA and 24/46 patients in IHA) underwent OGTT again after starting the treatment of PA.

Statistical analysis

All analyses were carried out using the JMP version 14.0 software (Statistical Analysis System Institute, Cary, NC, USA). Values are presented as the mean ± standard deviation. Categorical values were compared using a χ^2-test, and other values were analyzed by Student's t-test or the Mann–Whitney U-test. The changes in the PG and IRI after the treatment of PA were analyzed by the Wilcoxon signed-rank test. Multivariable logistic regression model was used to identify factors related to improvement of glucose intolerance after the treatment of PA. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of aldosterone-producing adenoma and idiopathic hyperaldosteronism

Characteristics of patients with APA and IHA are shown in Table 1. Patients with APA were significantly younger than those with IHA. The frequency of women was higher in IHA compared with APA. Significant differences were also observed in serum potassium concentration, PAC and PRA between the two groups. The detection of adrenal tumor on computed tomography scan was more common in APA than in IHA. There were no significant differences in the metabolic parameters; that is, fasting plasma glucose, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, body mass index and the percentage of central obesity between the two groups. In addition, there was no significant difference in the basal level of serum cortisol between the two groups.

PG and IRI levels in OGTT

The PG and IRI levels during OGTT in APA and IHA are shown in Figure 1. In fact, 46.4% (13/28) of APA patients and 52.3% (46/88) of IHA patients were categorized into the IGT or diabetes group (Table 2). There was no difference in the frequency of glucose intolerance between APA and IHA

Table 1 | Baseline characteristics of two primary aldosteronism subtypes

Parameter	APA (n = 28)	IHA (n = 88)	P
Male/female	16/12	29/59	0.024
Age (years)	48.1 ± 2.1	53.5 ± 1.2	0.026
BMI (kg/m^2)	24.9 ± 0.7	24.9 ± 0.4	0.98
Obesity (%)	50.0	48.9	0.92
Central obesity (%)	38.1 (8/21)	44.4 (31/71)	0.60
SBP (mmHg)	138.0 ± 3.0	137.5 ± 1.7	0.87
DBP (mmHg)	78.7 ± 2.2	78.8 ± 1.2	0.95
eGFR (mL/min/1.73 m^2)	85.3 ± 3.6	81.9 ± 2.1	0.41
TC (mg/dL)	186.9 ± 5.8	198.8 ± 3.3	0.24
TG (mg/dL)	132.6 ± 12.4	121.6 ± 7.0	0.44
LDL-C (mg/dL)	107.7 ± 5.4	114.1 ± 3.0	0.30
HDL-C (mg/dL)	52.7 ± 3.0	56.4 ± 1.7	0.27
FPG (mg/dL)	91.6 ± 2.3	92.6 ± 1.3	0.72
HbA1c (%)	5.5 ± 0.07	5.6 ± 0.04	0.065
K$^+$ (mEq/L)	2.86 ± 0.08	3.92 ± 0.05	<0.001
PAC (pg/mL)	503.1 ± 41.0	144.8 ± 23.2	<0.001
PRA (ng/mL/h)	0.22 ± 0.04	0.38 ± 0.02	<0.001
Cortisol (μg/dL)	14.1 ± 0.78	14.1 ± 0.44	0.97
Adrenal tumor on CT (%)	85.7	34.9	<0.001

Obesity was defined as body mass index (BMI) ≥25 kg/m^2. Central obesity was defined as waist circumference ≥85 cm and ≥90 cm for men and women, respectively. Data are expressed as the mean ± standard deviation. APA, aldosterone-producing adenoma; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimate glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; IHA, idiopathic hyperaldosteronism; LDL-C, low density lipoprotein cholesterol; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

($P = 0.83$). Although PG levels were similar in both subtypes, the IRI levels at 30 and 60 min were significantly lower in APA compared with IHA. The indices of insulin secretion and insulin sensitivity are shown in Table 2. Although significant differences were not observed in HOMA-β and HOMA-IR between the two subtypes, the insulinogenic index was significantly lower in APA than in IHA and the Matsuda index was significantly higher in APA than in IHA.

Transition of glucose metabolism after the treatment of primary aldosteronism

Transitions of OGTT subcategories after the treatment of PA in patients who were categorized into the IGT or diabetes group before the treatment of PA are shown in Figure 2. In detail, adrenalectomy was carried out in three patients with APA, and medical treatments were introduced in 24 patients with IHA. Among the medical treatments for IHA, one patient was prescribed with spironolactone (25 mg/day), and other patients were prescribed with eplerenone. The mean dose of eplerenone was 61.4 ± 25.3 mg/day. With these treatments, glucose tolerance was improved in two out of the three patients
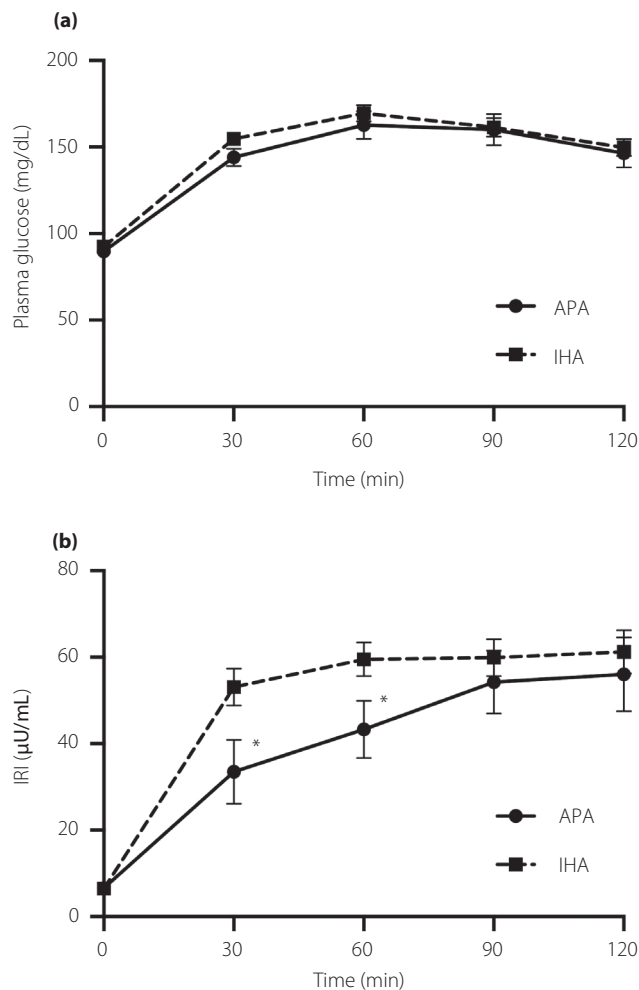
(a)

(b)

Figure 1 | Plasma glucose and insulin levels during oral glucose tolerance test in two primary aldosteronism subtypes. (a) Plasma glucose and (b) insulin (IRI) levels during 75-g oral glucose tolerance test in aldosterone-producing adenoma (APA; *n* = 28) and , idiopathic hyperaldosteronism (IHA; *n* = 88). Data are expressed as the mean ± standard deviation. *$P < 0.05$ versus IHA.

Table 2 | Indices of glucose metabolism in two primary aldosteronism subtypes

Parameter	APA (*n* = 28)	IHA (*n* = 88)	*P*
DM/IGT/NGT	3/10/15	9/37/42	0.83
PG (mg/dL)	143.5 ± 4.7	145.5 ± 2.7	0.71
IRI (μU/mL)	38.7 ± 4.7	48.0 ± 2.7	0.089
HOMA-β	90.6 ± 15.4	89.0 ± 8.7	0.93
Insulinogenic index	0.51 ± 0.12	0.78 ± 0.07	0.045
HOMA-IR	1.51 ± 0.18	1.47 ± 0.10	0.85
Matsuda index	8.09 ± 0.72	6.13 ± 0.42	0.022

Data are expressed as the mean ± standard deviation. APA, aldosterone-producing adenoma; DM, diabetes mellitus; HOMA-β, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment-insulin resistance; IGT, impaired glucose tolerance; IHA, idiopathic hyperaldosteronism; IRI, immunoreactive insulin; NGT, normal glucose tolerance; PG, plasma glucose.
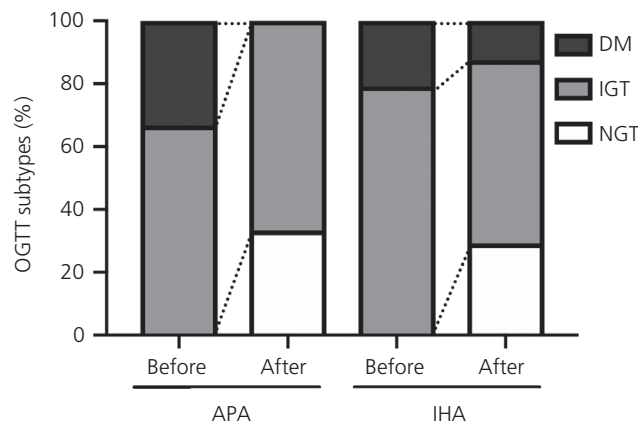

Figure 2 | Transitions of oral glucose tolerance test (OGTT) subcategories by primary aldosteronism treatments. Percentages of OGTT subcategories (diabetes [DM], impaired glucose tolerance [IGT] and normal glucose tolerance [NGT]) before and after primary aldosteronism treatments are shown in stacked bar graphs of each primary aldosteronism subtype (*n* = 3 for aldosterone-producing adenoma [APA] and *n* = 24 for idiopathic hyperaldosteronism [IHA]).

(66.6%) in APA, and 11 out of the 24 patients (45.8%) in IHA. Because of the limited number of APA cases who received OGTT after adrenalectomy, we further carried out analyses to evaluate the effects of PA treatment on the glucose metabolism within IHA. The PG and IRI levels during OGTT in IHA patients with improved glucose intolerance after the treatments of PA (improvement group) and patients with non-improved glucose intolerance after the treatment of PA (non-improvement group) are shown in Figure 3. Among the improvement group, the PG levels at 90 and 120 min were significantly decreased after the treatment. Furthermore, the post-challenge IRI levels from 30 to 90 min were slightly increased, and that at 120 min was significantly decreased after the treatment. Consequently, the time to peak insulin level was shifted to

90 min from 120 min. Among the non-improvement group, the PG levels at 0 and 60 min were rather increased after the treatment. The basal IRI level (0 min) was significantly increased, but the time to peak insulin level was not changed after the treatment. Table 3 shows the clinical characteristics of IHA patients with improved glucose intolerance after the treatments of PA. The presence of obesity or central obesity was significantly lower in the improvement group compared with the non-improvement group. No difference was observed in the dose of eplerenone between the two groups. The baseline indices of insulin secretion and insulin sensitivity of the improvement group and non-improvement group are shown in

Table 4. There were no significant differences in the baseline insulin secretion and insulin sensitivity between the two groups. A multivariable logistic regression model was used to identify parameters for predicting non-improvement of glucose intolerance after the treatment of PA, including sex, age, obesity, systolic blood pressure, serum potassium level and PAC. Inclusion of variables in the model was based on existing knowledge of risk factors for impaired glucose tolerance. The analysis showed that obesity was an independent and significant factor related to non-improvement of glucose intolerance after the treatment of PA in IHA patients (Table 5).

DISCUSSION

In previous studies, several mechanisms have been suggested regarding the association between hyperaldosteronism and dysregulated glucose homeostasis. Hypokalemia induced by hyperaldosteronism causes impaired insulin secretion[7]. In addition, aldosterone impairs glucose-stimulated insulin secretion through reactive oxygen species[24]. Furthermore, hyperaldosteronism is associated with impaired insulin sensitivity in the skeletal muscle[8]. Because of these mechanisms, PA is considered as an endocrine cause of diabetes[5], and several studies have reported an increased risk of diabetes in patients with PA[25,26]. For

instance, Akehi et al.[27] recently reported that the prevalence of diabetes in patients with PA was 21.6%, approximately twice in frequency of that in the general population. However, the difference in the pathogenesis of glucose intolerance among the subtypes of PA has not been fully elucidated. To the best of our knowledge, this is the first report focusing on the pathogenic difference of glucose intolerance between APA and IHA.

In the present study, both APA and IHA were found to be at a high risk of glucose intolerance. However, the pathogenesis was shown to be different between the two subtypes. For the development of glucose intolerance, insulin secretion impairment seems to play a more important role in APA compared with IHA. Previous studies have reported that APA has lower potassium levels and higher PAC compared with IHA, and these parameters might be beneficial in predicting the subtype of PA[28–30]. Similar to these previous studies, APA showed lower potassium levels and higher PAC in the present study. It is well known that hypokalemia impairs insulin secretion, and leads to glucose intolerance[31]. Furthermore, excessive aldosterone level is associated with decreased insulin secretion. Indeed, Luther et al.[24] suggested that aldosterone per se decreases glucose-stimulated insulin secretion in vivo. Fischer et al.[32] also reported that the aldosterone excess in PA affects
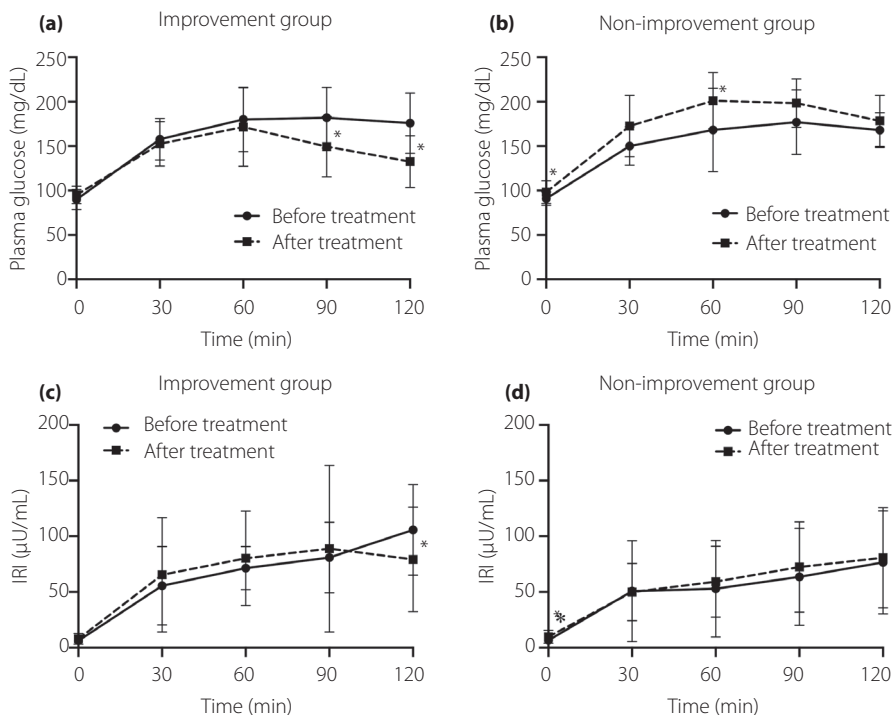

Figure 3 | Changes in plasma glucose and insulin levels during oral glucose tolerance test (OGTT) after the treatment of primary aldosteronism in idiopathic hyperaldosteronism patients. Plasma glucose levels during 75-g oral glucose tolerance test before and after primary aldosteronism treatment in the (a) glucose intolerance improvement group ($n = 11$) and (b) non-improvement group ($n = 13$). Plasma insulin (IRI) levels during 75-g oral glucose tolerance test before and after the treatment in the (c) glucose intolerance improvement group ($n = 11$) and (d) non-improvement group ($n = 13$). Data are expressed as the mean ± standard deviation. *$P < 0.05$ versus before the treatment.

Table 3 | Characteristics of idiopathic hyperaldosteronism patients whose glucose intolerance was improved after primary aldosteronism treatments

Parameter	Improvement group ($n = 11$)	Non-improvement group ($n = 13$)	P
Male/female	3/8	4/9	0.85
Age (years)	57.2 ± 2.9	61.8 ± 2.6	0.25
BMI (kg/m^2)	23.3 ± 1.01	26.0 ± 0.93	0.073
Obesity (%)	27.3	76.9	0.013
Central obesity (%)	12.5 (1/7)	60.0 (4/6)	0.033
eGFR (mL/min/1.73 m^2)	69.0 ± 4.0	75.8 ± 3.7	0.34
SBP (mmHg)	138.5 ± 5.3	130.7 ± 4.8	0.28
DBP (mmHg)	79.0 ± 2.6	76.5 ± 2.4	0.50
TC (mg/dL)	201.5 ± 9.5	187.3 ± 8.7	0.45
TG (mg/dL)	122.9 ± 20.7	133.0 ± 19.0	0.77
LDL-C (mg/dL)	119.1 ± 8.4	103.3 ± 7.8	0.25
HDL-C (mg/dL)	57.8 ± 5.2	57.4 ± 4.7	0.98
FPG (mg/dL)	92.9 ± 3.2	92.4 ± 2.9	0.81
HbA1c (%)	5.7 ± 0.10	5.6 ± 0.09	0.46
K$^+$, before treatment (mEq/L)	3.92 ± 0.15	3.95 ± 0.14	0.79
K$^+$, after treatment (mEq/L)	4.27 ± 0.13	4.36 ± 0.12	0.78
PAC, before treatment (pg/mL)	130.9 ± 94.4	236.2 ± 86.8	0.86
PAC, after treatment (pg/mL)	276.9 ± 94.5	391.7 ± 82.8	0.60
PRA, before treatment (ng/mL/h)	0.34 ± 0.04	0.35 ± 0.04	0.98
PRA, after treatment (ng/mL/h)	0.60 ± 0.11	0.68 ± 0.10	0.57
Cortisol, before treatment (µg/dL)	13.1 ± 1.2	15.2 ± 1.1	0.27
Treatment period in IHA (months)	40.9 ± 9.2	53.5 ± 8.3	0.40
Dose of eplerenone (mg/day)	63.6 ± 7.8	59.1 ± 7.8	0.68

Obesity was defined as body mass index (BMI) ≥25 kg/m^2. Central obesity was defined as waist circumference ≥85 cm and ≥90 cm for men and women, respectively. Data are expressed as the mean ± standard deviation. APA, aldosterone-producing adenoma; eGFR, estimate glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; IHA, idiopathic hyperaldosteronism; LDL-C, low density lipoprotein cholesterol; PAC, plasma aldosterone concentration; PRA, plasma renin activity; TC, total cholesterol; TG, triglyceride.

Table 4 | Baseline indices of glucose metabolism in the improvement group and non-improvement group of idiopathic hyperaldosteronism patients

Parameter	Improvement group ($n = 11$)	Non-improvement group ($n = 13$)	P
DM/IGT	3/8	1/12	0.19
PG (mg/dL)	157.1 ± 6.4	150.9 ± 5.8	0.71
IRI (µU/mL)	68.0 ± 9.3	49.7 ± 7.6	0.15
HOMA-β	138.2 ± 42.1	89.9 ± 40.3	0.60
Insulinogenic index	0.73 ± 0.18	0.71 ± 0.16	0.77
HOMA-IR	1.38 ± 0.19	1.48 ± 0.18	0.74
Matsuda index	5.11 ± 0.76	5.85 ± 0.72	0.48

Data are expressed as the mean ± standard deviation. DM, diabetes mellitus; HOMA-β, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment-insulin resistance; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; NGT, normal glucose tolerance; PG, plasma glucose.

the β-cell functions, namely the first-phase insulin secretion. To check the association of insulin secretion and insulin sensitivity with serum potassium level, we divided the patients to a hypokalemia group (K <3.5 mEq/L) and normo- and hyperkalemia group (K ≥3.5 mEq/L).

The insulinogenic index was significantly lower in the hypokalemia group, whereas no significant difference was observed in the Matsuda index between the two groups (hypokalemia vs normo- and hyperkalemia: $0.52 ± 0.10$ vs $0.72 ± 0.065$, $P = 0.046$ and $7.80 ± 1.03$ vs $7.31 ± 0.64$, $P = 0.69$, respectively). Likewise, we divided the patients into a high PAC group (PAC ≥140 pg/mL) and normal PAC group (PAC <140 pg/mL). The insulinogenic index was significantly lower in the high PAC group, whereas no significant difference was observed in the Matsuda index between the two groups (high PAC vs normal PAC: $0.55 ± 0.078$ vs $0.79 ± 0.077$, $P = 0.015$

Table 5 | Multivariable logistic regression model for predicting non-improvement of glucose intolerance after primary aldosteronism treatments in idiopathic hyperaldosteronism patients

Parameter	OR (95% CI)	P
Sex (male)	0.40 (0.016–10.1)	0.58
Age (years)	1.02 (0.87–1.19)	0.84
Obesity	29.3 (1.37–623.9)	0.031
SBP (mmHg)	0.96 (0.89–1.04)	0.35
K$^+$ (mEq/L)	2.12 (0.025–177.6)	0.74
PAC (pg/mL)	1.01 (0.97–1.05)	0.73

Obesity was defined as body mass index ≥25 kg/m^2. PAC, plasma aldosterone concentration; SBP, systolic blood pressure.

and 8.28 ± 0.77 vs 6.61 ± 0.76, $P = 0.13$, respectively). Although some of the previous studies report that hypokalemia and hyperaldosteronism are associated not only with impaired insulin secretion, but also with impaired insulin sensitivity[7,8], the present data suggest that hypokalemia and hyperaldosteronism influence on insulin secretion rather than insulin sensitivity. Thus, we hypothesized that the APA subtype could decrease insulin secretion as a result of the lower potassium level and higher PAC per se compared with IHA.

Ohno et al.[10] recently reported that patients with IHA tend to be obese, suggesting that obesity is possibly associated with the etiology of IHA. Some studies reported that the prevalence of metabolic syndrome was higher in patients with IHA compared with patients with APA[33]. Indeed, obesity has been suggested to induce hyperaldosteronism through the actions of adipocytokines; for example, activation of the sympathetic nervous system[10]. Shibayama et al.[34] reported that there was a positive association between PAC and visceral fat area in patients with IHA. In the present study, as shown in the lower Matsuda index, insulin sensitivity was lower in IHA compared with APA with no difference in the presence of either obesity or central obesity. However, as the presence of central obesity was slightly higher in IHA than in APA, the finding is possibly due to the small sample size in the present study. In addition, a statistical dissociation was observed between the Matsuda index and HOMA-IR in the present study. A possible reason for it is that the Matsuda index represents insulin resistance of both the liver and the skeletal muscle, whereas HOMA-IR basically represents insulin resistance of the liver and possibly underestimates insulin resistance of the skeletal muscle[35].

Of note, improved insulin secretion was observed in IHA patients with the improvement of glucose intolerance after PA treatment. It is of great interest that the time to peak insulin level was reduced by the PA treatment in the improvement group. We believe that such an improvement in the insulin secretion profile resulted in the decreased post-challenge plasma glucose levels in this group. In contrast, there was no change in the time to peak insulin level by the PA treatment in the non-improvement group. Indeed, the presence of obesity or central
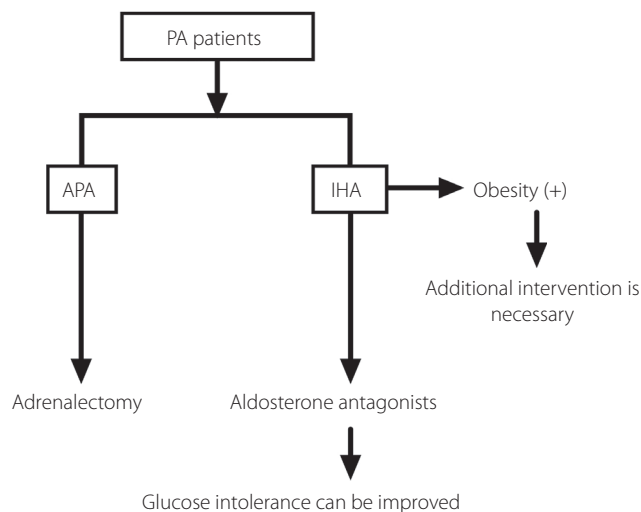

Figure 4 | Model describing possible approaches for improving glucose metabolism in primary aldosteronism (PA). Idiopathic hyperaldosteronism (IHA) patients without obesity might show improved glucose intolerance after the treatment of PA. In contrast, PA treatment alone could be insufficient to improve glucose intolerance for IHA patients with obesity and/or central obesity. APA, aldosterone-producing adenoma.

obesity was significantly higher in the non-improvement group. Accordingly, we suggest here that PA treatment alone could be insufficient to improve either glucose intolerance or insulin secretion profile in IHA associated with obesity or central obesity. For such PA patients, to improve glucose metabolism, an additional intervention to control bodyweight should be recommended (Figure 4), as not only aldosterone excess, but also other obesity-related factors, might play crucial roles in the development of glucose intolerance.

The present study had some limitations. First, this was a retrospective study at a single center, and the number of patients was limited. Second, we could not exclude the possibility of including patients with bilateral APA in patients who were diagnosed with IHA. Third, although all the patients in the present study underwent PA treatments after the diagnosis, the number of patients repeating the OGTT was limited. Thus, it would be difficult to conclude whether adrenalectomy can improve glucose metabolism in APA, because OGTT was repeated for just three APA patients.

In conclusion, although both APA and IHA showed a high prevalence of IGT and diabetes, each PA subtype seems to have a different pathogenesis of glucose intolerance; for example, insulin secretion impairment in APA and insulin resistance in IHA. In addition, IHA patients without obesity or central obesity are likely to improve their glucose metabolism after the treatments of PA. These findings are considered beneficial in addressing a better clinical strategy for the management of glucose intolerance associated with PA.

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