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Lipid Profiles in Primary Aldosteronism Compared with Essential Hypertension: Propensity-Score Matching Study

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Background: There has been controversy regarding the association between primary aldosteronism (PA) and dyslipidemia and few studies considered the effects of diabetes and renal function on lipid metabolism. We analyzed lipid profiles of PA patients and compared them to propensity-score (PS)-matched essential hypertension (EH) patients adjusting for glycemic status and renal function.
Methods: Patients who were diagnosed with PA using a saline-infusion test at Seoul National University Hospital from 2000 to 2018 were retrospectively analyzed. EH patients who had aldosterone-renin ratio (ARR) results were selected as controls. Covariates, including diabetes, were PS-matched for patients with PA, lateralized PA, non-lateralized PA, and high ARR to EH patients, respectively.
Results: Among a total of 80 PA and 80 EH patients, total cholesterol (TC) and triglyceride (TG) levels were significantly lower in the PA patients than in the EH patients (least-squares mean±standard error: 185.5±4.4 mg/dL vs. 196.2±4.4 mg/dL, $P=0.047$, for TC; and 132.3±11.5 mg/dL vs. 157.4±11.4 mg/dL, $P=0.035$, for TG) in fully adjusted model (adjusting for multiple covariates, including diabetes status, glycosylated hemoglobin level, and estimated glomerular filtration rate). There were no significant differences in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol levels between the two groups. According to increments in aldosterone levels, an increasing tendency of HDL-C and decreasing tendencies of TG and non-HDL-C were observed.
Conclusion: PA patients had lower TC and TG levels than EH patients, independent of glycemic status and renal function.

Keywords: Hyperaldosteronism; Metabolic syndrome; Dyslipidemias; Hypercholesterolemia; Glomerular filtration rate

INTRODUCTION

Primary aldosteronism (PA) is a disease caused by excessive production of aldosterone, independent of the renin-angiotensin system [1], and is known to account for 10% to 20% of hypertensive patients [2,3]. High aldosterone concentration in PA increases blood volume expansion, sodium retention, and urinary excretion of potassium, leading to hypertension and hypokalemia [4].

In addition to causing hypertension, PA has been reported to increase the risk of stroke, coronary artery disease, atrial fibril-

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lation, and heart failure, independent of hypertension, when compared to essential hypertension (EH) [5]. Aldosterone is considered to cause oxidative stress through mineralocorticoid receptors and increase collagen turnover, resulting in abnormal endothelial function, left ventricular thickening, and fibrosis in the kidney, heart and blood vessels, independent of hypertension [6].

Dyslipidemia is a critical contributor to atherosclerotic cardiovascular disease. Given the correlation between PA and cardiovascular disease, there might be higher possibility of dyslipidemia in PA. However, the lipid profile in patients with PA has not been well studied, and inconsistent results have been reported. In several studies comparing PA and EH patients, no significant differences in lipid profiles were observed between the two groups [7-10]. However, levels of plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were reportedly lower in PA patients than those in subjects with EH in other studies [11-13]. In particular, high-density lipoprotein cholesterol (HDL-C) levels were reportedly neither lower nor higher in PA patients. These inconsistent results may be attributed to the lack of adequate consideration of the various factors affecting dyslipidemia, such as insulin resistance, obesity, and renal function.

A high prevalence of glucose intolerance and/or diabetes has been reported in PA [7,12], and such metabolic disturbances can be associated with the changes in lipid profiles in PA. In addition, the contribution of excess aldosterone to renal impairment has been widely reported [14]. Chronic kidney disease is often associated with mild hyper-TG due to the accumulation of very-low-density lipoprotein and remnant lipoproteins in the circulation [15]. Therefore, it is necessary to consider metabolic conditions such as diabetes status and renal function, when assessing the effect of excess aldosterone on lipid profiles. However, diabetes and renal function have not been considered in previous studies. Therefore, in this study, we investigated the independent effect of PA on lipid profiles, after considering diabetes and renal function, among PA patients, patients with high aldosterone levels but not diagnosed with PA, and propensity-score (PS)-matched EH patients.

METHODS

Study subjects

Eligible patients were those aged ≥18 years, diagnosed with PA using the saline infusion test (SIT), and having results of lipid profiles, glycosylated hemoglobin (HbA1c), and estimated glomerular filtration rate (eGFR), and who had not been taking any lipid-lowering agent, mineralocorticoid antagonists, or amiloride before diagnosis. Patients with severe liver disease (Child-Pugh class ≥B) or uncontrolled hypothyroidism were excluded (Supplemental Figs. S1, S2). All PA patients had an elevated aldosterone-renin ratio (ARR, plasma aldosterone concentration [ng/dL] to plasma renin activity [ng/mL/hr] >20) and a positive SIT result. For comparison, patients with EH who had aldosterone and renin results, after excluding PA by their levels, were enrolled as a control group; patients with ARR >20 ng/dL per ng/(mL/hr) or aldosterone >10 ng/dL with renin <1 ng/mL/hr were excluded. In addition, patients with high ARR but negative confirmatory test (SIT or captopril challenge test) were also selected during the same period.

Diagnosis of the PA subtype was based on adrenal vein sampling with adrenocorticotropic hormone (cosyntropin) stimulation. The unilateral subtype of PA was defined as a lateralization index >4. The lateralization index was calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the non-dominant side [8]. On diagnosing PA subtype, patients with suspected autonomous cortisol secretion, defined as serum cortisol levels ≥1.8 μg/dL after a 1 mg dexamethasone suppression test, were excluded [16].

Outcomes

Lipid profiles, including TC, HDL-C, LDL-C, TG, and non-HDL-C, were analyzed as study outcomes. The analyzed lipid profile was used within 3 months of SIT or ARR measurement. In patients with PA, the lipid profiles measured before surgery or prior to specific medication such as mineralocorticoid antagonist or amiloride were analyzed. First, lipid profiles were compared between PA and matched EH patients who had undergone 1:1 PS-matching. Second, patients with lateralized PA, non-lateralized PA, and high ARR but negative confirmatory test were compared with matched EH patients who had undergone 1:1 PS-matching, respectively. Third, lipid profiles were analyzed by dividing all patients enrolled in this study into three percentiles according to aldosterone levels.

Statistical analysis

Continuous variables were expressed as mean±standard deviation or standard error for normally distributed variables and median (interquartile range [IQR]) for variables that did not follow a normal distribution. Categorical variables were presented as numbers and percentages. First, PA patients were PS-matched with EH patients. Second, instead of performing subgroup analyses for PS-matched PA patients, lateralized PA patients and

non-lateralized PA patients from the initial cohort were independently PS-matched again with EH patients. In addition, patients with high ARR but negative confirmatory test were independently matched with EH patients. All PS-matching analyses were performed in a 1:1 ratio, matched by age, sex, body mass index (BMI), and diabetes mellitus status. All eGFR values used in this study were calculated using the Modification of Diet in Renal Disease equation. Nearest neighbor methods were used with calipers measuring 0.1 the width of the PS logit, and an absolute standard mean difference (SMD) <0.1, was regarded as the cutoff for the optimal matching of each covariate [17,18].

Baseline characteristics and lipid profiles of each group were analyzed using the independent *t* test or one-way analysis of variance (ANOVA), and the Bonferroni multiple comparison test was performed for *post hoc* analysis. In addition, the Mann-Whitney test was performed for variables that did not have a normal distribution, even after log transformation. For multivariable analysis, analysis of covariance (ANCOVA) analysis was performed, adjusting for the following covariates: age, sex, BMI, HbA1c, diabetes mellitus, and eGFR. Multiple linear regression analyses with the continuous form of aldosterone tertiles were performed to calculate *P* for trends. *P* values <0.05 were considered to indicate statistical significance. R optmatch package (R version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB no. H-2002-128-1104). The need for patient consent was waived by the IRB because this was a retrospective study, and analyses were performed using de-identified data.

RESULTS

Baseline characteristics between PA and matched EH patients

After selecting the study subjects, a total of 80 PA patients and 80 PS-matched EH patients who were not taking lipid-lowering

Table 1. Baseline Characteristics and Lipid Profiles between Patients with PA and EH (PS-Matched Control) Who Were Not Taking Lipid-Lowering Agents

Characteristic	PA (*n*=80)	EH[a] (*n*=80)	*P* value	SMD
Age, yr[b]	51.7±11.2	51.7±14.4	0.583	0.001
Male sex	41 (51.2)	43 (53.8)	0.874	0.050
BMI, kg/m^2	25.2±3.7	25.3±3.6	0.851	0.030
Diabetes	16 (20.0)	17 (21.2)	1.000	0.031
Aldosterone, ng/dL[b]	28.2 (20.8–41.3)	14.4 (7.5–18.8)	<0.001	0.832
Renin activity, ng/mL/hr[b]	0.1 (0.1–0.3)	2.3 (1.3–5.2)	<0.001	0.564
ARR, ng/dL per ng/(mL/hr)[b]	198.8 (99.2–294.3)	5.3 (2.7–10.2)	<0.001	1.651
eGFR, mL/min/1.73 m^2[b]	75.7 (64.2–91.3)	68.1 (58.3–84.0)	0.033	0.263
Potassium, mEq/L	3.6±0.6	4.2±0.4	<0.001	1.216
HbA1c, %[b]	5.8±0.9	5.8±0.7	0.540	0.012
TC, mg/dL	187.0±32.1	198.2±34.4	0.036	0.336
HDL-C, mg/dL[c]	51.2±14.9	51.1±15.1	0.973	0.004
LDL-C, mg/dL	113.7±25.7	118.2±28.7	0.301	0.164
TG, mg/dL[c]	129.2±81.8	155.8±99.6	0.031	0.292
Non-HDL-C, mg/dL	135.9±31.3	146.9±34.9	0.038	0.332

Values are expressed as mean±standard deviation, number (%), or median (interquartile range). Variables of each group were compared by independent *t* test, Mann-Whitney test and chi-square test.
PA, primary aldosteronism; EH, essential hypertension; PS, propensity-score; SMD, standard mean difference; BMI, body mass index; ARR, aldosterone-renin ratio; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
[a]Controls were selected from essential hypertension group, matched (1:1) by age, sex, BMI, and diabetes mellitus, using PS-matching methods; [b]The Mann-Whitney test was performed on variables that do not follow the normal distribution; [c]Log-transformed.

agents were compared (Supplemental Fig. S1). The baseline characteristics of each group are presented in Table 1. There were no significant differences in PS-matching covariates, namely, age, sex, BMI, and the proportion of patients with diabetes, between the two groups, and their SMDs were all less than 0.1, indicating that matching was properly performed (Table 1).

In PA patients, aldosterone level was significantly higher (median, 28.2 ng/dL [IQR, 20.8 to 41.3] vs. 14.4 ng/dL [IQR, 7.5 to 18.8], $P<0.001$), renin activity was significantly lower (0.1 ng/mL/hr [IQR, 0.1 to 0.3] vs. 2.3 ng/mL/hr [IQR, 1.3 to 5.2], $P<0.001$), and ARR was significantly higher (198.8 ng/dL per ng/[mL/hr] [IQR, 99.2 to 294.3] vs. 5.3 ng/dL per ng/[mL/hr] [IQR, 2.7 to 10.2], $P<0.001$) than that in matched EH patients. The eGFR level was also significantly higher in PA patients (75.7 mL/min/1.73 m^2 [IQR, 64.2 to 91.3] vs. 68.1 mL/min/1.73 m^2 [IQR, 58.3 to 84.0], $P=0.033$). In addition, in the PA patients, potassium levels were significantly lower than the EH patients (3.6±0.6 mEq/L vs. 4.2±0.4 mEq/L, $P<0.001$).

Lipid profile differences between PA and matched EH patients

Without adjusting for covariates, TC (187.0±32.1 mg/dL vs. 198.2±34.4 mg/dL, $P=0.036$), TG (129.2±81.8 mg/dL vs. 155.8±99.6 mg/dL, $P=0.031$), and non-HDL-C levels (135.9±31.3 mg/dL vs. 146.9±34.9 mg/dL, $P=0.038$) were significantly lower in the PA patients than in the EH patients. There were no statistically significant differences in HDL-C and LDL-C levels between the two groups (Table 1).

In multivariable analyses, adjusted for age, sex, BMI, and diabetes mellitus, the results were similar to those of univariate analyses (Table 2). TC, TG, and non-HDL-C levels among PA patients were significantly lower than those of matched EH patients (least-squares mean±standard error: 185.0±4.2 mg/dL vs. 196.3±4.2 mg/dL, $P=0.033$, for TC; 134.9±10.9 mg/dL vs. 159.5±10.8 mg/dL, $P=0.033$, for TG; and 135.1±4.2 mg/dL vs. 146.0±4.1 mg/dL, $P=0.038$, for non-HDL-C). There were no significant differences in HDL-C and LDL-C levels between PA and EH patients.

Because eGFR was different between PA and EH patients and glucose control status could affect lipid profiles, further analysis was performed by adjusting for HbA1c and eGFR values. On comparing PA and EH patients, the magnitude of the difference in TC and TG was similar after adjusting for HbA1c values (185.2±4.4 mg/dL vs. 196.5±4.4 mg/dL, $P=0.034$, for TC; and 132.5±11.4 mg/dL vs. 157.1±11.3 mg/dL, $P=0.033$, for TG) and it was reduced yet still statistically significant when eGFR values were additionally adjusted for (185.5±4.4 mg/dL vs. 196.2±4.4 mg/dL, $P=0.047$, for TC; and 132.3±11.5 mg/dL vs. 157.4±11.4 mg/dL, $P=0.035$, for TG). On comparing non-HDL-C levels, after adjusting for HbA1c level, the magnitude of the difference did not change considerably (134.3±4.4 mg/dL vs. 145.3±4.3 mg/dL, $P=0.038$); however, when eGFR values were additionally adjusted for, no significant difference was observed between the two groups (134.7±4.4 mg/dL vs. 144.7±4.3 mg/dL, $P=0.060$) (Table 2).

Baseline characteristics and lipid profiles between lateralized PA, non-lateralized PA, high ARR, and matched EH patients

To perform subgroup analyses, PS-matching of the following

Table 2. Multivariable Analysis for Lipid Profiles between Patients with PA and EH (PS-Matched Control) Who Were Not Taking Lipid-Lowering Agents

	Least-squares mean		*P* value		
	PA	EH	P^a	P^b	P^c
TC, mg/dL	185.5±4.4	196.2±4.4	0.033	0.034	0.047
HDL-C, mg/dL	50.7±1.8	51.4±1.7	0.796[d]	0.801[d]	0.711[d]
LDL-C, mg/dL	112.0±3.6	116.0±3.6	0.283	0.284	0.352
TG, mg/dL	132.3±11.5	157.4±11.4	0.033[d]	0.033[d]	0.035[d]
Non-HDL-C, mg/dL	134.7±4.4	144.7±4.3	0.038	0.038	0.060

Values are expressed as least-squares mean±standard error. Analysis of covariance (ANCOVA) analyses were performed adjusted for age, sex, body mass index (BMI), and diabetes mellitus (DM). Further analysis was performed by correcting glycated hemoglobin (HbA1c), and HbA1c & estimated glomerular filtration rate (eGFR) respectively. Estimated mean shown in the table is the value adjusted for age, BMI, sex, DM, HbA1c, and eGFR.
PA, primary aldosteronism; EH, essential hypertension; PS, propensity-score; TC, total cholesterol; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; TG, triglyceride.
[a]Adjusted for Age+BMI+Sex+DM; [b]Adjusted for Age+BMI+Sex+DM+HbA1c; [c]Adjusted for Age+BMI+Sex+DM+HbA1c+eGFR; [d]Log-transformed.

Table 3. Baseline Characteristics and Lipid Profiles between Patients with Lateralized PA, Non-Lateralized PA, High ARR, and EH (PS-Matched Control) Who Were Not Taking Lipid-Lowering Agents

Characteristic	Lateralized PA (*n*=49)	EH[a] (*n*=49)	*P* value	Non-lateralized PA (*n*=34)	EH[a] (*n*=34)	*P* value	High ARR (SIT or CCT negative) (*n*=35)	EH[a] (*n*=35)	*P* value
Age, yr	51.1±10.7	51.2±14.6	0.968	52.8±12.3	51.6±15.6	0.811[b]	52.2±13.0	52.6±12.7	0.638[b]
Male sex	20 (40.8)	20 (40.8)	1.000	22 (64.7)	21 (61.8)	1.000	19 (54.3)	19 (54.3)	1.000
BMI, kg/m^2	25.0±3.8	25.1±3.2	0.841	25.4±3.3	25.3±3.5	0.967	26.3±3.8	26.3±4.0	0.999
Diabetes	10 (20.4)	10 (20.4)	1.000	7 (20.6)	8 (23.5)	1.000	8 (22.9)	8 (22.9)	1.000
Aldosterone, ng/dL	43.6±30.1	17.1±12.9	<0.001[c]	26.3±10.9	19.9±23.1	<0.001[c]	20.5±7.6	12.7±6.8	<0.001[c]
Renin activity, ng/mL/hr	0.1 (0.1–0.2)	2.3 (1.4–4.7)	<0.001[b]	0.2 (0.1–0.4)	2.3 (1.4–5.8)	<0.001[b]	0.2 (0.1–0.5)	2.2 (1.4–5.2)	<0.001[b]
ARR, ng/dL per ng/(mL/hr)	244.0 (149.1–369.0)	6.4 (2.6–10.6)	<0.001[b]	152.8±106.3	6.3±4.1	<0.001	112.7±98.8	6.5±4.6	<0.001
eGFR, mL/min/1.73 m^2	75.4 (63.6–93.4)	67.3 (57.6–82.7)	0.152[b]	85.2 (69.3–91.1)	65.2 (57.1–85.4)	0.007[b]	84.6 (74.1–102.4)	66.9 (57.5–89.2)	0.013[b]
Potassium, mEq/L	3.5±0.6	4.3±0.4	<0.001	3.8±0.5	4.4±0.6	<0.001	4.2±0.5	4.3±0.5	0.872
HbA1c, %	5.6 (5.4–5.9)	5.6 (5.4–6.1)	0.669[b]	5.6 (5.4–5.9)	5.6 (5.3–6.2)	0.777[b]	5.7 (5.4–6.0)	5.8 (5.5–6.2)	0.268[b]
TC, mg/dL	186.1±36.6	203.0±37.7	0.027	188.2±27.1	194.7±36.3	0.410	194.4±34.9	197.9±35.7	0.693
HDL-C, mg/dL	54.4±14.6	54.6±15.7	0.957[c]	48.1±14.0	46.6±9.8	0.603	49.1±13.9	53.5±127	0.171
LDL-C, mg/dL	113.3±30.1	123.8±30.9	0.094	115.5±21.2	118.4±29.2	0.639	123.6±27.0	118.6±28.8	0.489[c]
TG, mg/dL	110.5±72.4	144.0±83.1	0.014[c]	141.8±87.4	163.3±121.8	0.405[c]	145.8±111.2	143.6±91.4	0.972[c]
Non-HDL-C mg/dL	131.7±35.2	148.4±35.2	0.022	140.2±28.3	148.1±38.7	0.336	145.2±32.1	143.9±33.9	0.876

Values are expressed as mean±standard deviation, number (%), or median (interquartile range). Variables of each group were compared by independent *t* test, Mann-Whitney test and chi-square test.

PA, primary aldosteronism; ARR, aldosterone-renin ratio; EH, essential hypertension; PS, propensity-score; ARR, aldosterone-renin ratio; SIT, saline infusion test; CCT, captopril challenge test; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; TC, total cholesterol; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

[a]Controls were selected from essential hypertension group, matched (1:1) by age, sex, BMI, and diabetes mellitus, using propensity score matching methods; [b]The Mann-Whitney test was performed on variables that do not follow the normal distribution; [c]Log-transformed.

subgroups was independently conducted: lateralized PA, non-lateralized PA and high ARR with negative confirmatory test. (Supplemental Fig. S2). Lateralized PA (n=49), non-lateralized PA (n=34), and high ARR with negative confirmatory test patients (n=35) were compared with 1:1 PS-matched EH patients, respectively (Table 3). PS-matching covariates were successfully matched in every analysis, and no statistical differences were observed (all SMD <0.1, and all P values >0.05) (Supplemental Table S1). ARRs were significantly higher in all groups than in matched EH groups (all P<0.001), and the extents were substantially elevated in the following order: the high ARR, non-lateralized PA, and lateralized PA patients (112.7±98.8, 152.8±106.3, and 244.0 ng/dL per ng/[mL/hr] [IQR, 149.1 to 369.0], respectively).

On comparing the lateralized PA patients with the matched EH patients, the TC (186.1±36.6 mg/dL vs. 203.0±37.7 mg/dL, P=0.027), TG (110.5±72.4 mg/dL vs. 144.0±83.1 mg/dL, P=0.014), and non-HDL-C (131.7±35.2 mg/dL vs. 148.4±35.2 mg/dL, P=0.022) levels were found to be significantly lower in the lateralized PA patients. However, there were no significant differences in the HDL-C and LDL-C levels. In addition, there was no significant difference in lipid profile between the non-lateralized PA and matched EH patients, as well as between the high ARR with negative confirmatory test and matched EH patients.

As regards total patients with PA, multivariable analyses, adjusted for age, sex, BMI, and diabetes mellitus, were performed between lateralized PA, non-lateralized PA, and high ARR and corresponding matched EH patients for each subtype (Table 4). TC (least-squares mean±standard error 181.5±6.1 mg/dL vs. 198.1±6.0 mg/dL, P=0.030), TG (120.8±12.0 mg/dL vs. 153.4±12.0 mg/dL, P=0.010), and non-HDL-C (130.7±5.7 mg/dL vs.

Table 4. Multivariable Analysis for Lipid Profiles between Patients with Lateralized PA, Non-Lateralized PA, High ARR, and EH (PS-Matched Control) Who Were Not Taking Lipid-Lowering Agents

	Least-squares mean		*P* value		
	PA or high ARR	EH	P^a	P^b	P^c
Lateralized PA					
TC, mg/dL	182.8±6.4	198.7±6.6	0.030	0.028	0.042
HDL-C, mg/dL	51.5±2.4	52.9±2.5	0.923[d]	0.771[d]	0.606[d]
LDL-C, mg/dL	111.7±5.2	121.3±5.5	0.101	0.094	0.130
TG, mg/dL	116.5±12.5	146.5±13.1	0.010[d]	0.014[d]	0.019[d]
Non-HDL-C mg/dL	131.3±6.0	145.8±6.3	0.025	0.027	0.049
Non-lateralized PA					
TC, mg/dL	179.6±6.4	187.2±6.1	0.342	0.325	0.341
HDL-C, mg/dL	49.1±2.1	47.3±2.0	0.426	0.429	0.477
LDL-C, mg/dL	110.7±4.9	112.6±4.7	0.563	0.537	0.754
TG, mg/dL	114.2±20.7	150.5±19.8	0.320[d]	0.316[d]	0.179[d]
Non-HDL-C mg/dL	130.5±6.5	140.0±6.3	0.240	0.224	0.247
High ARR[e]					
TC, mg/dL	191.3±7.3	191.8±7.5	0.709	0.853	0.955
HDL-C, mg/dL	49.8±2.5	54.9±2.7	0.146	0.134	0.111
LDL-C, mg/dL	120.2±5.6	112.1±5.7	0.433[d]	0.274[d]	0.305[d]
TG, mg/dL	139.6±20.7	133.0±21.5	0.978[d]	0.963[d]	0.824[d]
Non-HDL-C mg/dL	141.6±6.6	136.7±6.8	0.876	0.692	0.553

Values are expressed as least-squares mean±standard error. Analysis of covariance (ANCOVA) analyses were performed adjusted for age, sex, body mass index (BMI), and diabetes mellitus (DM). Further analysis was performed by correcting glycated hemoglobin (HbA1c), and HbA1c & estimated glomerular filtration rate (eGFR) respectively. Estimated mean shown in the table is the value adjusted for age, BMI, sex, DM, HbA1c, and eGFR.
PA, primary aldosteronism; ARR, aldosterone-renin ratio; EH, essential hypertension; PS, propensity-score; TC, total cholesterol; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; TG, triglyceride.
[a]Adjusted for Age+BMI+Sex+DM; [b]Adjusted for Age+BMI+Sex+DM+HbA1c; [c]Adjusted for Age+BMI+Sex+DM+HbA1c+eGFR; [d]Log-transformed; [e]High ARR represents patients with high ARR with negative confirmatory tests.

Table 5. Multiple Regression Analysis for Lipid Profiles According to Aldosterone Levels among PA+High ARR+EH Who Were Not Taking Lipid-Lowering Agents

	Aldosterone concentrations			*P* value for trend		
	1st tertile	2nd tertile	3rd tertile	*P*[a]	*P*[b]	*P*[c]
TC, mg/dL	193.6±4.7	195.0±4.9	184.4±4.7	0.228	0.123	0.128
HDL-C, mg/dL	48.5±1.9	52.0±1.9	53.4±1.8	0.009[d]	0.030[d]	0.031[d]
LDL-C, mg/dL	114.7±3.8	119.2±4.0	110.8±3.7	0.474[d]	0.384[d]	0.385[d]
TG, mg/dL	160.9±12.8	140.1±13.5	126.4±12.7	0.007[d]	0.004[d]	0.004[d]
Non-HDL-C mg/dL	145.0±4.5	143.2±4.7	130.9±4.5	0.025	0.015	0.016

Values are expressed as least-squares mean±standard error. Analysis of covariance (ANCOVA) adjusted for age, sex, body mass index (BMI), diabetes status, glycated hemoglobin (HbA1c), and estimated glomerular filtration (eGFR) were performed for estimated mean, and multiple linear regression analyses with continuous form of aldosterone tertiles were performed to calculate *P* for trends. Estimated mean shown in the table is the value adjusted for age, BMI, sex, diabetes mellitus (DM), HbA1c, and eGFR.
PA, primary aldosteronism; ARR, aldosterone-renin ratio; EH, essential hypertension; TC, total cholesterol; HDL-C, high-density lipoproteins cholesterol; LDL-C, low-density lipoproteins cholesterol; TG, triglyceride.
[a]Adjusted for Age+BMI+Sex+DM; [b]Adjusted fir Age+BMI+Sex+DM+HbA1c; [c]Adjusted for Age+BMI+Sex+DM+HbA1c+eGFR; [d]Log-transformed.

147.0±5.7 mg/dL, *P*=0.025) levels of lateralized PA patients were significantly lower than those of matched EH patients. There were no significant differences in lipid profiles between non-lateralized PA and matched EH patients, as well as between high ARR and matched EH patients.

Further analysis was performed by adjusting for HbA1c and eGFR values. On comparing the TC, TG, and non-HDL-C values between lateralized PA and matched EH patients, HbA1c adjustment did not affect the result. Estimated GFR adjustment decreased the significance; however, the difference remained statistically significant (Table 4).

Lipid profiles according to aldosterone levels

The lipid profiles were analyzed by dividing the patients into three percentiles according to aldosterone levels (Table 5). As the aldosterone level increased, HDL-C tended to increase significantly after adjusting for age, sex, BMI, and diabetes status (least-squares mean±standard error: 47.3±1.7 mg/dL vs. 51.0±1.7 mg/dL vs. 53.2±1.8 mg/dL, *P*=0.009). On the other hand, TG and non-HDL-C level tended to decrease significantly with increasing aldosterone level (160.0±11.9 mg/dL vs. 141.5±12.1 mg/dL vs. 129.7±12.0 mg/dL, *P*=0.007, for TG; and 145.6±4.4 mg/dL vs. 143.3±4.4 mg/dL vs. 133.0±4.4 mg/dL, *P*=0.025, for non-HDL-C). Additional analyses were performed by adjusting for HbA1c and eGFR values. On comparing HDL-C values, the magnitude of the difference decreased when HbA1c values were adjusted for (48.4±1.9 mg/dL vs. 52.0±1.9 mg/dL vs. 53.4±1.8 mg/dL, *P*=0.030). Further adjustment for the eGFR value slightly reduced the magnitude of the difference; nonetheless, the difference remained statistically significant (48.5±1.9 mg/dL vs. 52.0±1.9 mg/dL vs. 53.4±1.8 mg/dL, *P*=0.031) (Table 5).

DISCUSSION

In this study, we investigated the effect of PA on lipid profiles among Korean patients with PA by comparing them to PS-matched EH patients. TC and TG levels were significantly lower in PA patients after matching covariates, including diabetes status and eGFR. In particular, among patients with lateralized PA, TC, TG, and non-HDL-C concentrations were lower than those in matched EH patients. Whereas HDL-C increased, TG and non-HDL-C decreased as the tertile of aldosterone concentration increased.

It is well known that PA is associated with cardio-cerebrovascular complications, and dyslipidemia can contribute to their cause [19,20]. Therefore, studies have attempted to evaluate the association between PA and dyslipidemia. Inconsistent results have been reported regarding the effect of PA on dyslipidemia. In this study, we found lower TC, TG, and non-HDL-C levels among PA patients than EH patients. This is partly consistent with the results of previous reports. In a German cohort, PA patients showed lower levels of TC, LDL-C, and TG and higher levels of HDL-C than EH patients [12]. In another study including 20 patients with PA, PA was associated with lower concentrations of LDL and HDL particles and TG [11]. Different results have been reported in studies analyzing lipid profiles according to the type of PA. A retrospective study conducted in

France showed no difference in lipid profiles between lateralized and non-lateralized PA [8]. On the other hand, in another study conducted in the Czech Republic that retrospectively analyzed aldosterone producing adenoma (APA) and idiopathic hyperaldosteronism patients, HDL-C was higher in patients with APA, and TG was lower [21].

In the present study, the TC and TG were lower in PA and lateralized PA patients than EH patients, even after adjusting with glycemic status and renal function. In addition, when they were divided and analyzed according to aldosterone level, it was found that as the aldosterone level increases, the HDL-C increases and the TG and non-HDL-C decreases. From these results, lipid profile change might not play a role in the increased risk of cardiovascular disease in PA.

There is no evidence that aldosterone is directly involved in lipid metabolism. Instead, aldosterone is considered to indirectly affect lipid metabolism through mechanisms that induce insulin resistance or increase eGFR. Aldosterone is known to increase insulin resistance by inhibiting insulin signaling and insulin-stimulated glucose uptake in adipocytes, skeletal muscle, and vascular smooth muscle cells [22,23]. In the insulin-resistant state, HDL-C decreases due to increased hepatic lipase activity and increased levels of TG-rich lipoprotein [24]. However, in this study and previous reports, PA was associated with lower TG and higher HDL-C levels or had no significant results. In patients with PA, an increase in blood pressure and plasma volume can cause glomerular hyperfiltration [25,26], although evidence on the association between the development of hyperfiltration and PA remains controversial [27-29]. Hypertriglyceridemia is common in chronic kidney disease. Although the underlying mechanism has not been completely elucidated, decreased activity of lipoprotein lipase (LPL) is considered a major mechanism [30]. Therefore, an increase in eGFR in PA [25,26] can be associated with higher LPL activity, and it can increase TG-rich-lipoprotein clearance and reduce plasma TG levels. Taken together, lower TG levels in PA are largely attributable to increased eGFR rather than insulin resistance. In this study, the statistical significance of lower TC, TG, and non-HDL-C in PA and lateralized PA patients was reduced or disappeared when eGFR was additionally adjusted for. However, because TC and TG remained lower after adjusting for glycemic status and eGFR, other mechanisms may also contribute to these results.

It has been reported that a significant proportion (10% to 20%) of PAs accompany subclinical hypercortisolism [31,32]. Despite the controversy, the association between bilateral PA and obesity or higher BMI [21,33] has been reported and the association has been explained by accompanying subcortical hypercortisolism. In this analysis, however, patients with suspected autonomous cortisol secretion, defined as serum cortisol levels $\geq$1.8 μg/dL after a 1 mg dexamethasone suppression test, were excluded. In addition, as the aldosterone levels were significantly higher in lateralized PA than non-lateralized PA and the difference in lipid profiles according to the increase of aldosterone level was significant, the aldosterone levels themselves seemed to be important in the difference in lipid profiles.

To investigate the association between hyperaldosteronism and lipid profiles, it was essential to set up an appropriate control group. For this, we performed PS-matching methods, and the covariates that can influence lipid metabolism, including diabetes status, sex, age, and BMI, were properly matched (SMD of all covariates <0.1) (Table 1, Supplemental Table S1). In addition, we enrolled subjects with EH among patients who had aldosterone and renin results to exclude undiagnosed PA. Furthermore, beyond the simple comparison of PA and EH patients, various approaches were used to increase the validity of the study: subtypes of PA and patients with high ARR with negative confirmatory tests were also individually matched with EH patients, and analyses according to aldosterone levels were performed. As observed in the baseline characteristics of the study population, aldosterone level, ARR, and potassium level were consistent with the expected clinical results, thus supporting the reliability of our study. Unlike previous studies that did not consider diabetes status and renal function, which both affect the lipid profile, this study considered the effect of diabetes, HbA1c, and eGFR using multivariable analyses.

This study has several limitations. There are reports that subclinical Cushing syndrome (SCS) and PA are related [31], and SCS is also known to be associated with dyslipidemia [33]; however, the effect of SCS was not completely excluded because overnight dexamethasone test was not performed all PA subjects. Other metabolic components influencing lipid profiles like waist circumference or percentage of body fat were not considered. If additional results such as apolipoprotein (apo) A1, apo B, and lipoprotein(a) were analyzed other than the lipid profile presented in this study, it would have been more helpful to understand the change in lipid metabolism in PA. However, further analysis was not possible due to the limited information. Also, since this was a retrospective study, the fasting time could not be accurately determined, therefore, the lipid profiles may not have been measured in the fasting state. However, blood tests are usually performed in the fasting state according to gen-

eral hospital practice and there was no person with a co-measured glucose concentration of 200 mg/dL or more, so it was likely that the blood tests were performed in the fasting state that did not significantly affect the TG concentration. In addition, due to the relatively small number of study subjects, statistical power could have been inadequate to evaluate the differences in lipid profiles between groups. However, a comparable control group was established through PS-matching, and consistent results were obtained.

In conclusion, PA patients had lower TC and TG levels than EH patients, independent of glycemic status and renal function. Further studies are required to investigate additional mechanisms may involve in lipid metabolism in PA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: M.K.M. Acquisition, analysis, or interpretation of data: S.J.M., H.N.J., J.H.K., M.K.M. Drafting the work or revising: S.J.M., H.N.J., J.H.K., M.K.M. Final approval of the manuscript: S.J.M., H.N.J., J.H.K., M.K.M.

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REFERENCES

1. Vaidya A, Mulatero P, Baudrand R, Adler GK. The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. Endocr Rev 2018;39:1057-88.
2. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann Intern Med 2020;173:10-20.
3. Mantero F, Mattarello MJ, Albiger NM. Detecting and treating primary aldosteronism: primary aldosteronism. Exp Clin Endocrinol Diabetes 2007;115:171-4.
4. Rossier BC, Baker ME, Studer RA. Epithelial sodium transport and its control by aldosterone: the story of our internal environment revisited. Physiol Rev 2015;95:297-340.
5. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2018;6:41-50.
6. Brown NJ. Aldosterone and end-organ damage. Curr Opin Nephrol Hypertens 2005;14:235-41.
7. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, et al. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J Clin Endocrinol Metab 2006;91:454-9.
8. Matrozova J, Steichen O, Amar L, Zacharieva S, Jeunemaitre X, Plouin PF. Fasting plasma glucose and serum lipids in patients with primary aldosteronism: a controlled cross-sectional study. Hypertension 2009;53:605-10.
9. Stehr CB, Mellado R, Ocaranza MP, Carvajal CA, Mosso L, Becerra E, et al. Increased levels of oxidative stress, subclinical inflammation, and myocardial fibrosis markers in primary aldosteronism patients. J Hypertens 2010;28:2120-6.
10. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, et al. Prevalence and clinical manifestations of primary aldosteronism encountered in primary care practice. J Am Coll Cardiol 2017;69:1811-20.
11. Berends AMA, Buitenwerf E, Gruppen EG, Sluiter WJ, Bakker SJL, Connelly MA, et al. Primary aldosteronism is associated with decreased low-density and high-density lipoprotein particle concentrations and increased GlycA, a pro-inflammatory glycoprotein biomarker. Clin Endocrinol (Oxf) 2019;90:79-87.
12. Hanslik G, Wallaschofski H, Dietz A, Riester A, Reincke M, Allolio B, et al. Increased prevalence of diabetes mellitus and the metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry. Eur J Endocrinol 2015;173:665-75.
13. Reincke M, Fischer E, Gerum S, Merkle K, Schulz S, Pallauf A, et al. Observational study mortality in treated primary aldosteronism: the German Conn's registry. Hypertension 2012;60:618-24.
14. Kawashima A, Sone M, Inagaki N, Takeda Y, Itoh H, Kurihara I, et al. Renal impairment is closely associated with plasma aldosterone concentration in patients with primary aldosteronism. Eur J Endocrinol 2019;181:339-50.
15. Kwan BC, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney

disease. J Am Soc Nephrol 2007;18:1246-61.
16. Bochud M, Nussberger J, Bovet P, Maillard MR, Elston RC, Paccaud F, et al. Plasma aldosterone is independently associated with the metabolic syndrome. Hypertension 2006;48:239-45.
17. Siniscalchi C, Quintavalla R, Rocci A, Riera-Mestre A, Trujillo-Santos J, Surinach JM, et al. Statin and all-cause mortality in patients receiving anticoagulant therapy for venous thromboembolism. Data from the RIETE registry. Eur J Intern Med 2019;68:30-5.
18. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33:1242-58.
19. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014;11:276-89.
20. Yaghi S, Elkind MS. Lipids and cerebrovascular disease: research and practice. Stroke 2015;46:3322-8.
21. Somloova Z, Widimsky J Jr, Rosa J, Wichterle D, Strauch B, Petrak O, et al. The prevalence of metabolic syndrome and its components in two main types of primary aldosteronism. J Hum Hypertens 2010;24:625-30.
22. Corry DB, Tuck ML. The effect of aldosterone on glucose metabolism. Curr Hypertens Rep 2003;5:106-9.
23. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep 2013;15:59-70.
24. Verges B. Lipid modification in type 2 diabetes: the role of LDL and HDL. Fundam Clin Pharmacol 2009;23:681-5.
25. Ribstein J, Du Cailar G, Fesler P, Mimran A. Relative glomerular hyperfiltration in primary aldosteronism. J Am Soc Nephrol 2005;16:1320-5.
26. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL, et al. Long-term renal outcomes in patients with primary aldosteronism. JAMA 2006;295:2638-45.
27. Reincke M, Rump LC, Quinkler M, Hahner S, Diederich S, Lorenz R, et al. Risk factors associated with a low glomerular filtration rate in primary aldosteronism. J Clin Endocrinol Metab 2009;94:869-75.
28. Rossi GP, Bernini G, Desideri G, Fabris B, Ferri C, Giacchetti G, et al. Renal damage in primary aldosteronism: results of the PAPY Study. Hypertension 2006;48:232-8.
29. Wu VC, Yang SY, Lin JW, Cheng BW, Kuo CC, Tsai CT, et al. Kidney impairment in primary aldosteronism. Clin Chim Acta 2011;412:1319-25.
30. Kaysen GA. New insights into lipid metabolism in chronic kidney disease. J Ren Nutr 2011;21:120-3.
31. Fujimoto K, Honjo S, Tatsuoka H, Hamamoto Y, Kawasaki Y, Matsuoka A, et al. Primary aldosteronism associated with subclinical Cushing syndrome. J Endocrinol Invest 2013;36:564-7.
32. Hiraishi K, Yoshimoto T, Tsuchiya K, Minami I, Doi M, Izumiyama H, et al. Clinicopathological features of primary aldosteronism associated with subclinical Cushing's syndrome. Endocr J 2011;58:543-51.
33. Tauchmanova L, Rossi R, Biondi B, Pulcrano M, Nuzzo V, Palmieri EA, et al. Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocrinol Metab 2002;87:4872-8.