Effects of Altered Calcium Metabolism on Cardiac Parameters in Primary Aldosteronism

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Background: Increasing evidence supports interplay between aldosterone and parathyroid hormone (PTH), which may aggravate cardiovascular complications in various heart diseases. Negative structural cardiovascular remodeling by primary aldosteronism (PA) is also suspected to be associated with changes in calcium levels. However, to date, few clinical studies have examined how changes in calcium and PTH levels influence cardiovascular outcomes in PA patients. Therefore, we investigated the impact of altered calcium homeostasis caused by excessive aldosterone on cardiovascular parameters in patients with PA.

Methods: Forty-two patients (mean age 48.8 ± 10.9 years; 1:1, male:female) whose plasma aldosterone concentration/plasma renin activity ratio was more than 30 were selected among those who had visited Severance Hospital from 2010 to 2014. All patients underwent adrenal venous sampling with complete access to both adrenal veins.

Results: The prevalence of unilateral adrenal adenoma (54.8%) was similar to that of bilateral adrenal hyperplasia. Mean serum corrected calcium level was 8.9 ± 0.3 mg/dL (range, 8.3 to 9.9). The corrected calcium level had a negative linear correlation with left ventricular end-diastolic diameter (LVEDD, $\rho = -0.424$, $P = 0.031$). Moreover, multivariable regression analysis showed that the corrected calcium level was marginally associated with the LVEDD and corrected QT (QTc) interval ($\beta = -0.366$, $P = 0.068$ and $\beta = -0.252$, $P = 0.070$, respectively).

Conclusion: Aldosterone-mediated hypercalciuria and subsequent hypocalcemia may be partly involved in the development of cardiac remodeling as well as a prolonged QTc interval, in subjects with PA, thereby triggering deleterious effects on target organs additively.

Keywords: Hyperaldosteronism; Hypocalcemia; Heart diseases; Parathyroid hormone

INTRODUCTION

Primary aldosteronism (PA) is the most frequent form of secondary hypertension (HTN) [1]. PA accounts for up to 20% of patients with resistant HTN [2]. Moreover, one study demonstrated that about 13% of a normotensive cohort had biochemi-

cally confirmed PA, and that these patients were at a higher risk for developing incident HTN [3]. Prolonged elevated aldosterone concentrations are known to be associated with an increased risk of myocardial infarction, atrial fibrillation, stroke, and chronic kidney disease [4,5]. In addition, an excess of aldosterone can itself lead to a greater number of cardiovascular complications, independent of blood pressure (BP), compared to that seen with essential HTN [4,6]. Beyond its role in affecting BP and intravascular volume, PA may influence metabolic alterations [7] and oxidative stress, thereby damaging target organs [8,9].

Parathyroid hormone (PTH) plays an important role in bone and mineral metabolism, and its secretion from the parathyroid gland is dependent on serum calcium levels [10]. Aldosterone may impact calcium and mineral homeostasis by enhancing renal loss of calcium and magnesium, thereby contributing to hypocalcemia and subsequent secondary hyperparathyroidism (SHPT) [11,12]. An increasing body of evidence has shown an interplay between the renin-angiotensin-aldosterone system (RAAS) and PTH, which may potentiate cardiovascular risk in certain heart diseases, such as congestive heart failure [13,14]. However, there is a lack of data on how hypocalcemia practically affects cardiovascular parameters, such as electrocardiography (ECG) or echocardiography, in PA patients.

Given this background, we hypothesized that the changes in calcium metabolism that occur in PA may effect cardiac structural or functional changes independent of plasma aldosterone levels.

METHODS

Subjects

Forty-two patients with PA (mean age 48.8±10.9 years) were enrolled from among all patients who visited the HTN clinic at Severance Hospital from 2010 to 2014. The inclusion criteria were as follows: a plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio of more than 30; a diagnosis of PA confirmed using a saline loading test; available blood samples for measuring PTH levels. A positive result was defined as a post-saline loading PAC of over 8.5 ng/dL [15]. All patients underwent sequential adrenal venous sampling (AVS) with complete access to both adrenal veins. Moreover, serum PTH levels were measured by immunoradiometric assays; the reference range was 10 to 57 pg/mL. The measurement of serum 25-hydroxyvitamin D (25(OH)D) levels was performed in 40 patients (95.2%). The present study protocol was reviewed

and approved by the Institutional Review Board of Yonsei University College of Medicine, and all participants signed consent forms (approval no. 4-2012-0544). All investigations were performed in accordance with the principles of the Declaration of Helsinki.

Subtype classification

In all patients, adrenal computed tomography (CT) was conducted in three phases with a 64-channel multidetector CT scanner (Discovery CT750HD, GE Healthcare, Milwaukee, WI, USA) before AVS. The CT and AVS protocols were the same as described in our previous study [16]. All patients underwent C-arm CT (Axiom Artis dTA, Siemens, Erlangen, Germany)-assisted sequential bilateral AVS with 100% successful access to both adrenal veins during continuous intravenous infusion of tetracosactide (Cynacten, Dalim Biotech, Seoul, Korea). C-arm CT was used because it improves accuracy of right adrenal vein catheterization during AVS. All AVS procedures were performed in the angiography room in which C-arm CT was available. When C-arm CT images revealed the proper catheter position, blood sampling was conducted. Vein samples were obtained at least 30 minutes after initiation of intravenous tetracosactide administration. Adequate catheterization during AVS was defined as a cortisol ratio in blood sampled from the adrenal vein and inferior vena cava of equal to or more than 3:1. In addition, when the adrenal venous blood cortisol-corrected aldosterone ratio was greater than 2.6 after tetracosactide stimulation, a unilateral lesion was considered to be present on the high-value side [15].

Assessment of cardiac structure, function, and electrical activity

Echocardiography was conducted in 28 subjects (66.7%). Comprehensive echocardiographic assessments were conducted by three experienced sonographers, who had no knowledge of the clinical data, using commercially available ultrasound systems (Sonos 5500, Philips Medical Systems, Andover, MA, USA; or Vivid Seven, GE Vingmed Ultrasound, Horten, Norway). All echocardiographic parameters were measured according to recommendations from the American Society of Echocardiography [17]. The echocardiography protocol was the same as described in our previous study [8]. The following parameters were evaluated: left ventricular ejection fraction (LVEF, %), left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), end-diastole interventricular septum diameter (IVSd, mm), end-diastole left ventricular (LV)

posterior wall diameter (PWd, mm), left ventricular mass index (LVMI, g), left atrial volume index (LAVI, mL/m^2), early and late mitral flow velocities (E and A, m/sec), deceleration time (DT) of E velocity (msec), and the ratio of E to early diastolic mitral annular velocity (E/E' ratio). Systolic function was measured by LVEF. Additionally, the presence of cardiac remodeling regarding structural abnormality was assessed using LVEDD, LVESD, IVSd, PWd, LV mass, LVMI, and LAVI; E and A velocities, DT, and E/E' ratio were used as parameters for diastolic function. ECG was carried out in all patients. Twelve-lead ECGs were recorded by digital ECG instruments (General Electric Healthcare, Milwaukee, WI, USA), and we investigated the corrected QT (QTc) interval as a marker for representing the risk of arrhythmia in patients with PA.

Statistical analysis

Statistical analyses were conducted using IBM SPSS version 23.0 for Windows (IBM Co., Armonk, NY, USA). Due to the small number of patients in our study, some data were analyzed using nonparametric tests. Student t tests and chi-square tests were used to compare differences in continuous and categorical

variables, respectively, between unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH) patients. The relationships between each echocardiographic parameter and PAC or corrected calcium level were determined by using the Spearman partial correlation after adjusting for age and sex. Also, multivariate regression analyses were used to examine the associations between corrected calcium level and each echocardiographic parameter or QTc interval in those with PA. P values <0.05 were considered statistically significant.

RESULTS

The baseline characteristics of all subjects are presented in Table 1. There were 21 males and 21 females in our cohort. The prevalence of unilateral APA (54.8%) was similar to that of BAH. The mean BP was 149/91 mm Hg, and mean duration of HTN was about 7.6 years. In addition, mean PTH and serum calcium

Table 1. Baseline Characteristics

Characteristic	Total (n=42)
Age, yr	48.8±10.9
Sex, male/female	21/21
HTN duration, yr	7.6±7.9
Systolic blood pressure, mm Hg	149.3±18.5
Diastolic blood pressure, mm Hg	90.8±12.2
Heart rate, bpm	74.0±11.4
Serum potassium, mmol/L	3.53±0.52
tCO$_2$, mmol/L	28.7±3.3
PAC, ng/dL	33.8±23.5
PRA, ng/mL/hr	0.24±0.24
ARR	341.8±951.4
PAC after saline loading test, ng/dL	19.6±16.3
PTH, pg/mL	56.1±26.5
25(OH)D, ng/mL	12.8±6.2
Corrected calcium, mg/dL	8.9±0.3
QTc interval, msec	431.7±23.9

Values are expressed as mean±standard deviation.
HTN, hypertension; tCO$_2$, total carbon dioxide; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-renin ratio; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; QTc, corrected QT.

Table 2. Differences in Aldosterone and Corrected Calcium Levels between Patients with APA and BAH

Variable	APA (n=23)	BAH (n=19)	P value
Age, yr	46.5±11.5	51.5±9.8	0.146
Sex, male/female	9/14	12/7	0.121
HTN duration, yr	6.6±4.6	9.1±11.0	0.406
Systolic blood pressure, mm Hg	149.7±18.8	148.9±18.6	0.901
Diastolic blood pressure, mm Hg	89.8±13.1	92.0±11.1	0.574
Heart rate, bpm	72.3±10.7	75.5±12.2	0.438
Serum potassium, mmol/L	3.46±0.57	3.63±0.43	0.314
tCO$_2$, mmol/L	29.1±3.6	28.2±2.9	0.458
PAC, ng/dL	42.6±27.0	23.2±12.1	0.004
PRA, ng/mL/hr	0.23±0.22	0.25±0.26	0.857
ARR	527.1±1,233.4	90.4±60.6	0.141
PAC after saline loading test, ng/dL	27.2±18.6	10.4±4.9	<0.001
PTH, pg/mL	61.9±30.7	49.1±18.8	0.122
25(OH)D, ng/mL	12.1±5.0	13.6±7.3	0.451
Corrected calcium, mg/dL	8.8±0.3	9.0±0.3	0.036
QTc interval, msec	439.4±25.3	422.3±18.6	0.019

Values are expressed as mean±standard deviation.
APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; HTN; hypertension; tCO$_2$, total carbon dioxide; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-renin ratio; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; QTc, corrected QT.

levels were approximately 56.1 pg/mL and 8.9 mg/dL, respectively.

Differences in aldosterone and corrected calcium levels between APA and BAH patients

Differences in PAC, serum PTH, and calcium levels between APA and BAH patients are described in Table 2. Even though the differences in BP, serum potassium, and the PAC/PRA ratio between APA and BAH subjects were not definite, there were significant differences in baseline PAC and PAC levels after the saline loading test between the two groups. Moreover, serum corrected calcium levels were significantly lower in APA subjects when compared with BAH subjects (8.8 mg/dL vs. 9.0 mg/dL, respectively); however, no meaningful differences were found for PTH or serum 25(OH)D levels between the two groups. In addition, patients with APA showed a more prolonged QTc interval than those with BAH.

Associations between PAC and corrected calcium levels and echocardiographic parameters in patients with PA

We evaluated whether aldosterone or hypocalcemia could affect each echocardiographic parameter in patients with PA. As shown in Table 3, PAC was negatively correlated with LVEF

and DT ($\rho=-0.396$, $P=0.046$ and $\rho=-0.422$, $P=0.036$, respectively), but showed positive correlations with LVESD and A velocity ($\rho=0.396$, $P=0.045$ and $\rho=0.474$, $P=0.022$, respectively) even after the adjustments for age and sex, indicating that aldosterone can have an impact on cardiac remodeling, such as structural abnormalities and diastolic function. Meanwhile, the corrected calcium level had a negative linear correlation with LVEDD ($\rho=-0.424$, $P=0.031$).

Associations between corrected calcium levels and echocardiographic parameters or the QTc interval in patients with PA

To confirm whether alterations in calcium homeostasis associated with excessive aldosterone exert influence on echocardiographic parameters or the QTc interval in subjects with PA, multivariable regression analyses were performed (Table 4). As aldosterone excess is known to lead to metabolic alkalosis as well as increased urinary calcium loss, corrected calcium, PAC, and total CO_2 were used for the adjustment. As a result, the negative association between serum corrected calcium levels and LVEDD remained marginally significant, even after adjusting for PAC and total CO_2 ($\beta=-0.366$, $P=0.068$). Also, corrected calcium levels showed a trend towards being negatively associ-

Table 3. Association between Aldosterone or Corrected Calcium Levels and Echocardiographic Parameters in Patients with Primary Aldosteronism

Variable	Correlation coefficient (PAC)	*P* value	Correlation coefficient (corrected calcium)	*P* value
Parameters for structural abnormality				
LVEF, %	−0.396	0.046[a]	−0.079	0.700
LVEDD, mm	0.270	0.182	−0.424	0.031[a]
LVESD, mm	0.396	0.045[a]	−0.227	0.266
IVSd, mm	−0.120	0.559	0.120	0.561
PWd, mm	−0.104	0.614	−0.123	0.549
LV mass, g	0.182	0.405	−0.153	0.487
LVMI, g/m²	0.037	0.867	−0.351	0.101
LAVI, mL/m²	0.050	0.813	−0.094	0.656
Parameters for diastolic function				
E velocity, m/sec	0.209	0.316	−0.150	0.475
A velocity, m/sec	0.474	0.022[a]	0.251	0.248
Deceleration time, msec	−0.422	0.036[a]	−0.242	0.244
E/E' ratio	0.250	0.228	−0.065	0.759

PAC, plasma aldosterone concentration; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSd, interventricular septum diameter; PWd, posterior wall diameter; LV, left ventricular; LVMI, left ventricular mass index; LAVI, left atrial volume index.
[a]$P<0.05$, after adjusting for age and sex.

Table 4. Factors Associated with LVEDD and the QTc Interval in Patients with Primary Aldosteronism

Parameter	β	95% CI	*P* value
LVEDD			
PAC, ng/dL	0.373	–0.015 to –0.161	0.099
Corrected calcium, mg/dL	–0.366	–9.925 to 0.389	0.068
tCO₂	–0.477	–1.158 to –0.024	0.042
QTc interval			
PAC, ng/dL	0.574	0.288 to –0.872	<0.001
Corrected calcium, mg/dL	–0.252	–40.466 to 1.680	0.070
tCO₂	–0.148	–3.228 to 1.030	0.301

LVEDD, left ventricular end-diastolic diameter; QTc, corrected QT; CI, confidence interval; PAC, plasma aldosterone concentration; tCO₂, total carbon dioxide.

ated with the QTc interval, although the relationship between corrected calcium levels and the QTc interval was only marginally significant ($\beta=-0.252$, $P=0.070$). The explanation powers (R-Square) of each model were 0.246 in the model of LVEDD and 0.391 in the model for QTc interval, respectively.

DISCUSSION

Recently, the significance of HTN and osteoporosis as public health problems has been emphasized, because the elderly population is rapidly rising all over the world. Aldosterone excess has been found to be associated with cardiovascular complications and organ damage [4,18]. Monticone et al. [18] showed that patients with PA were not only at an increased risk of cardiovascular diseases, including atrial fibrillation, coronary artery disease, heart failure, LV hypertrophy, and stroke, but also of metabolic disorders, such as diabetes mellitus and metabolic syndrome, compared with patients with essential HTN. Furthermore, increasing evidence has shown that PA is a risk factor for fractures, independent of BP [19,20], and contributes to detrimental effects on bone quality rather than bone mineral density via changes in mineral homeostasis [21]. In this regard, it is important to understand the effects of changes in calcium and PTH levels on cardiovascular outcomes in PA patients.

Calcium, which is a crucial structural component of bone and a major regulator in myocardial contraction, plays a number of essential roles in the normal physiological process of our body, including various cellular signaling cascades [22]. A meta-analysis recently reported that circulating calcium is related to vascular disease and mortality [23]. Foley et al. [24] also had shown

that a hazard ratio of stroke (1.37; 95% confidence interval, 1.28 to 1.46) according to standard deviation of corrected calcium level in a prospective and community-based study has increased. In addition, primary hyperparathyroidism (PHPT), which is usually characterized by hypercalcemia, has been associated with increased mortality, as well as cardiovascular morbidity [25]. Interestingly, the hypertensive aspect of PHPT is known to be linked to excessive aldosterone levels. The level of PTH is positively associated with aldosterone levels in PHPT; preoperative PTH levels over 100 ng/mL may be an independent predictor for abnormally elevated PAC [26]. Barkan et al. [27] also reported the case of a 60-year-old woman with PHPT exhibiting HTN and hypokalemia, similar to that seen in PA.

Furthermore, negative structural cardiovascular remodeling by PA might be related to elevated levels of PTH [28]. Cumulative evidence points to a bidirectional interaction between PTH and aldosterone, which can aggravate target organ damage [29]. PTH can increase aldosterone secretion from the adrenal gland not only directly, but also indirectly by activating the RAAS [30,31]. In the setting of chronic heart failure, secondary hyperaldosteronism may cause salt retention and SHPT due to urinary loss of calcium and magnesium [11]; in PA, hypercalciuria and hypocalcemia caused by excessive aldosterone stimulate the secretion of PTH, which, in turn, triggers aldosterone secretion [11,12]. Chronic mineralocorticoidism can cause oxidative stress and endothelial dysfunction, which can result in damage to vessels and cardiomyocytes [32]. Meanwhile, PTH can have deleterious effects on the heart: it can stimulate cardiomyocyte hypertrophy by activating protein kinase A or C [33] and induce cardiac arrhythmias through calcium overloading [34]. PTH-mediated calcium overloading has also been linked to an induction of oxidative stress in the mitochondria of cardiomyocytes, thereby contributing to necrosis and fibrosis of the heart [28]. These mechanisms may help explain the finding that aldosterone and PTH mutually affect cardiovascular mortality risk, as reported by Tomaschitz et al. [35]. However, although increasing evidence has demonstrated that hyperparathyroidism can lead to deleterious consequences for heart failure [14,29], few clinical studies have examined how alterations in calcium metabolism impact cardiovascular parameters in patients with PA.

In this study, APA patients had significantly lower serum corrected calcium levels and more prolonged QTc intervals than those with BAH, even though the differences in PTH levels between the two groups were not found. In a previous study, Ceccoli et al. [36] reported a higher level of PTH in the APA group than in the BAH group, although the statistical difference in PTH

levels between the two groups was not observed. Moreover, considering that APA patients usually have higher aldosterone levels than BAH patients, our inconsistent results regarding PTH levels may be due to the small number of subjects used in the current study. The next question was how aberration in calcium homeostasis regarding aldosterone excess affects each echocardiographic parameter or QTc interval in patients with PA.

According to our previous study [8], various inflammatory markers in relation to the oxidative stress in PA can affect some of echocardiographic parameters which reflect cardiac structure (LAVI, LVESD, IVSd, and LV mass) and diastolic function (A and E' velocities). On the other hand, this study showed that PAC was related to LVEF, LVESD, A velocity, and DT after adjusting for age and sex. In addition, the corrected calcium level was negatively correlated with LVEDD after adjusting for age and sex ($\rho=-0.424$, $P=0.031$), suggesting that aldosterone-induced hypocalcemia may have an influence on structural abnormalities in patients with PA. Intriguingly, despite the small number of population, multivariable regression analyses also demonstrated that corrected calcium levels showed a trend towards being negatively associated with LVEDD, even after adjustment for confounding factors ($\beta=-0.366$, $P=0.068$). We could observe such possibility that corrected calcium levels may aggravate structural abnormalities, thereby developing cardiac remodeling.

As an aforementioned previous study showed, atrial fibrillation had the highest odds ratio among the cardiovascular complications of PA patients [18]. Excessive aldosterone can influence mineral homeostasis [37], and sodium excretion is correlated with urinary calcium [38]. Additionally, hypercalciuria in hyperaldosteronism might be attributed to reduced sodium reabsorption in aldosterone-insensitive tubular areas [39]. Therefore, we speculated that altered calcium metabolism accompanied by aldosterone excess might play an important role in raising the risk of arrhythmias, including atrial fibrillation, although the negative association between corrected calcium levels and QTc interval was only marginally significant ($\beta=-0.252$, $P=0.070$).

To our knowledge, this is the first clinical study to analyze how changes in calcium levels impact cardiovascular parameters using ECG and echocardiography in patients with PA. Our data support the hypothesis that altered calcium homeostasis due to aldosterone excess might act as a potential aggravating factor for the development of cardiovascular complications and ultimately triggering deleterious effects on target organs. However, our study also has some limitations. First, this study has a cross-sectional design. Thus, it is difficult to confirm causality

between factors. Second, the sample size of this study was small. That might be why we could not observe significant associations between corrected calcium levels and LVEDD or QTc interval after adjusting for confounding factors. However, our result is quite valuable that these relationships were marginally significant in spite of the small number of population. Additionally, statistic problems such as multicollinearity of the multivariable regression analyses were not found, although the explanation power of these models was somewhat low. Third, we did not evaluate urine calcium or serum and urine magnesium levels. Considering mean value of serum 25(OH)D in this study, most of patients with PA may have vitamin D deficiency. Particularly, urinary calcium excretion may be very helpful to gain insight into the effects of aberrations in serum calcium, together with elevated PTH levels, on clinical cardiac outcomes in PA patients. Finally, echocardiography was conducted by three sonographers. Hence, inter-individual variations among their results are likely.

In conclusion, although the associations between corrected calcium levels and LVEDD or QTc interval were only marginally significant, our results suggest that aldosterone-mediated hypercalciuria and subsequent hypocalcemia may be in part involved in the development of structural cardiovascular remodeling and a prolonged QTc interval, thereby exacerbating target organ damage additively in subjects with PA. Therefore, a future, large, well-designed research study with long-term follow-up is required to explain the effects of altered calcium homeostasis on adverse cardiovascular outcomes in PA patients.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conceptualization: J.S.L., Y.R. Data curation: J.S.L., Y.R. Methodology: S.P., S.I.P., Y.T.O., Y.R. Formal analysis: J.S.L., M.H.Y. Writing (original draft preparation): J.S.L., P.Y.L. Writing (review and editing): J.S.L., N.H., Y.R.

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