Elevated Myoglobin in Patients With Primary Aldosteronism: A Cross-Sectional Study

Bing Kang1,2, Chuan Peng3, Kanran Wang1, Ying Song1, Yi Yang1, Linqiang Ma1, Mei Mei1, Jinbo Hu1, Shumin Yang1, Fei-Fei Wu4* and Qifu Li1*

1 Department of Endocrinology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, 2 Department of Clinical Nutrition, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, 3 The Chongqing Key Laboratory of Translational Medicine in Major Metabolic Diseases, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, 4 Department of Endocrinology, Affiliated Heping Hospital, Changzhi Medical College, Changzhi, China

Objectives: Primary aldosteronism (PA) is characterized by the autonomous excessive production of aldosterone in the adrenal cortex. Aldosterone is associated with damages to heart muscle and skeletal muscle. The purpose of this study was to evaluate serum levels of muscle injury markers and their associated factors in patients with primary aldosteronism.

Methods: We retrospectively enrolled subjects with PA and essential hypertension (EH) who had completed testing for serum high sensitivity troponin T (hs-TnT), creatine kinase isoenzyme MB (CK-MB) and myoglobin from the database of the Chongqing Primary Aldosteronism Study (CONPASS). Univariate and multivariate linear regression analyses were performed to analyze the influencing factors of myocardial injury markers.

Results: In total, 278 patients with PA and 445 patients with EH were enrolled in this study. Compared with EH patients, serum concentrations of hs-TnT [7.0 (4.0–12.0) vs. 6.0 (3.0–11.0) ng/L; p=0.005] and myoglobin [24.2 (21.0–38.1) vs. 21.8 (21.0–31.9) mg/L; p=0.023] were significantly higher among PA patients, while no significant difference of CK-MB was found between two groups [1.4 (1.0–2.0) vs. 1.3 (0.9–1.9) μg/L; p=0.154]. Univariate linear regression analysis showed that myoglobin was negatively correlated with serum potassium (β=-0.31; p<0.01) and positively correlated with plasma aldosterone concentration (β=0.40; p<0.01) in the PA group, while no significant correlation was found between hs-TnT and biochemical parameters. After adjusting for multiple confounders, myoglobin was negatively correlated with serum potassium (β=-0.15; p<0.05) and positively correlated with plasma aldosterone concentration (β=0.34; p<0.01) in the PA group.

Conclusions: The serum level of myoglobin was significantly increased in PA patients, and myoglobin was independently correlated with plasma aldosterone concentration.

Keywords: primary aldosteronism, markers, myoglobin, high sensitivity troponin T, creatine kinase isoenzyme MB
INTRODUCTION

Primary aldosteronism (PA) is characterized by the autonomous excessive production of aldosterone in the adrenal cortex, resulting in sodium retention, potassium excretion, increased blood volume, and a suppressed renin-angiotensin system (1). The typical clinical manifestations of PA are hypertension with or without hypokalemia (2–4). A recent study has indicated that the prevalence of PA among hypertension is 5-10% (5). Patients with PA have a higher risk of cardiovascular events, kidney damage and all-cause mortality than those with essential hypertension (EH) who are matched for age, sex, and blood pressure (6). Excessive aldosterone concentrations promote the onset and progression of cardiovascular diseases through various mechanisms, such as chronic vascular fluid retention, endothelial dysfunction, target organ inflammation and fibrosis (7).

Cardiac troponin T (TnT), creatine kinase isoenzyme MB (CK-MB) and myoglobin are widely used as cardiac injury markers (8, 9). Previous studies have shown that CK-MB and myoglobin are mainly distributed in the myocardium and skeletal muscle, and increase after damage to the myocardium or skeletal muscle cells, and hs-TnT is not only significantly elevated in acute coronary syndrome, but also reflects chronic myocardial injury or subclinical myocardial injury of unknown causes (10). hs-TnT, CK-MB and myoglobin are associated with chronic diseases such as diabetes and end-stage renal disease (11–15). Previous study showed that aldosterone is associated with damages to heart and skeletal muscle cells (16–19), while very few studies have evaluated serum levels of muscle injury markers in PA patients.

The present study aimed to compare serum levels of hs-TnT, CK-MB, myoglobin between patients with PA and EH, and analyze whether these markers correlated with clinical parameters such as aldosterone, which may facilitate seeking for biomarkers of hyperaldosteronemia related myocardium injury.

SUBJECTS AND METHODS

Study Population

We retrospectively enrolled patients diagnosed with PA and EH patients from the database of the Chongqing Primary Aldosteronism Study (CONPASS) (20–23) at the First Affiliated Hospital of Chongqing Medical University in China from November 2013 to January 2020. The inclusion criteria were as follows: patients aged 18 to 75 years; patients who had completed testing for serum hs-TnT, CK-MB and myoglobin. The exclusion criteria were as follows: 1) other known causes of secondary hypertension; 2) acute cardiovascular events within 3 months, including myocardial infarction and angina pectoris; 3) chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m², which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24); 4) acute or chronic heart failure (according to the New York Heart Association functional classification) (25, 26); 5) chronic obstructive pulmonary disease.

Clinical information, including medical history was collected through physician interviews. All subjects had undergone a physical examination including measurement of the height, weight and blood pressure. Hypokalemia was defined as a serum potassium level <3.5 mmol/L. Antihypertensive medications are showed as defined daily dose (DDD), which is the assumed average maintenance dose per day (27). Patients with cardiovascular diseases (CVD) 3 months before enrollment were considered with preexisting CVD. Target organ damage is defined as the presence of left ventricular hypertrophy at echocardiography and/or microalbuminuria (28). The local ethics committee approved the protocol, and the informed consent was obtained from all the participants.

Screening and Confirmatory Tests for PA

Before screening and confirmatory tests, antihypertensive medication was withdrawn or changed according to the Endocrine Society’s clinical practice guideline (1). Only non-dihydropyridine calcium channel blockers, terazosin, and doxazosin were allowed for uncontrolled hypertension. For screening, blood samples for plasma renin concentration (PRC) and the plasma aldosterone concentration were collected in the morning after the subjects were out of bed and maintained an upright position for at least 2 hours. Aldosterone-to-renin ratio (ARR) was calculated as plasma aldosterone concentration divided by PRC. ARR>20 pg·mL⁻¹/μIU·mL⁻¹ (27 pmol·L⁻¹/μIU·mL⁻¹) was considered a positive screening test (29). Patients who tested positive for ARR or negative but were strongly suspected of having PA were subjected to the confirmatory tests, while those who tested negative were not considered PA.

Confirmatory tests were performed as described in the current guidelines (1, 30), and PA was considered if any of the following criteria were met: 1) plasma aldosterone concentration > 110 pg/mL (305 pmol/L) after the captopril challenge test (CCT) (22); 2) plasma aldosterone concentration >80 pg/mL (221 pmol/L) after the infusion of 2 L normal saline in the recumbent position (22) or >85 pg/mL (235 pmol/L) in the seated position (21); 3) plasma aldosterone concentration > 60 pg/mL (166 pmol/L) on the fourth day of the fludrocortisone suppression test (FST).

Biochemical Measurements

Blood samples were collected to measure plasma aldosterone concentration, PRC, hs-TnT, CK-MB and myoglobin. Blood electrolytes were measured using an indirect ion selective electrode method and a Hitachi 7600-020 machine. hs-TnT, CK-MB and myoglobin were measured at 37°C using the electrochemiluminescence method, the instrument used was Roche E602, and the manufacturer’s kit was from Roche. Plasma aldosterone concentration and PRC were measured using the automatic chemiluminescence immunoassay (DiaSorin, Liaison, Italy), the detection range of plasma aldosterone concentration was 2.2~100 ng/dL, and the differences were 2.4%~4.8% and 4.4%~6.7% for inter-batch and intra-batch samples, respectively. The detection range of PRC was 0.13~0.53 mU/L, and the intrabatch and interbatch differences were 1.2%~3.7% and 2.9%~12.8%, respectively.
Statistical Analysis

SPSS 22.0 analysis software was used for statistical analysis. The measurement data were tested for normality and homogeneity of variance. Normally distributed variables were expressed as means ± standard deviation, nonnormally distributed variables as medians (interquartile range), and categorical variables as absolute values and percentages. Independent sample t test was used to compare the normally distributed data between the two groups, and χ² test was used to compare the counting data. Univariate linear regression was used to analyze the correlation between the three markers and the clinical/biochemical parameters of the enrolled subjects. P<0.05 indicated a statistically significant difference.

RESULTS

Characteristics of the Study Participants

The demographic, clinical and biological characteristics of the study population are summarized in Table 1. In total, 278 patients with PA and 445 patients with EH were enrolled in the present study. No significant difference was found in age, sex, BMI, diabetes, preexisting CVD, hs-CRP, or CK-MB between the PA and EH groups (p>0.05). Compared with EH patients, the SBP (153±20 vs. 146±23 mmHg; p<0.001), DBP (92±14 vs. 89±16 mmHg; p=0.01), DDD [1.5 (1–2) vs. 1 (0–2); p<0.001], duration of hypertension [7 (2–13) vs. 3 (0–8) years; p<0.001], serum creatinine (Scr) [71 (58–89) vs. 68 (57–83) μmol/L; p=0.045], history of hypokalemia (74.1% vs. 31.2%; p<0.001), plasma aldosterone concentration [270.0 (192.0–401.0) vs. 116.0 (72.3–171.0) pg/mL; p<0.001], ARR [100.3 (33.2–319.2) vs. 7.2 (3.2–21.7) pg·mL⁻¹/μIU·mL⁻¹; p<0.001], hs-TnT [7.0 (4.0–12.0) vs. 6.0 (3.0–11.0) ng/μL; p=0.005] and myoglobin [24.2 (21.0–38.1) vs. 21.8 (21.0–31.9) μg/L; p=0.023] were significantly higher in patients with PA. The proportion of target organ damage (31.7% vs. 15.1%; p<0.001) was higher in PA patients. The serum potassium concentration [3.3 (2.9–3.8) vs. 3.9 (3.6–4.2) μmol/L; p<0.001] and PRC [2.5 (0.9–7.0) vs. 12.8 (5.1–32.2) μIU/mL; p<0.001] were lower in PA patients.

hs-TnT, CK-MB and Myoglobin With Correlative Factors

Univariate linear regression analysis showed that myoglobin was negatively correlated with serum potassium (β=-0.31; p<0.01), and positively correlated with plasma aldosterone concentration (β=0.40; p<0.01) and ARR (β=0.37; p<0.01) in the PA group, while no significant correlation was found with age, SBP, DBP, DDD, duration of hypertension, the proportion of diabetes, preexisting CVD, target organ damage or serum creatinine concentration(p>0.05). None of the three markers (hs-TnT, CK-MB and myoglobin) were significantly associated with SBP, DBP, duration of hypertension, serum creatinine concentration, serum potassium concentration, plasma aldosterone concentration or ARR in the EH group (p>0.05) (Table 2).

After adjusting for age, sex, BMI, SBP, DBP, DDD, duration of hypertension, the proportion of diabetes, preexisting CVD, and target organ damage, multivariate linear regression analysis showed that myoglobin was negatively correlated with serum potassium (β=-0.15; p<0.05), and positively correlated with plasma aldosterone concentration (β=0.34; p<0.01), while no significant correlation was observed between hs-TnT and serum potassium or plasma aldosterone concentration in the PA group (p>0.05). No correlation was found between the three markers (hs-TnT, CK-MB and myoglobin) and serum potassium or plasma aldosterone concentration in the EH group (p>0.05) (Table 3).

### TABLE 1 | Demographic and clinical characteristics of the patient cohorts.

| Characteristics | PA (n=278) | EH (n=445) | P-value |
|----------------|-----------|-----------|---------|
| Age (years)    | 51 ± 12   | 51 ± 14   | 0.497   |
| Sex (women, %) | 58.3%     | 55.1%     | 0.441   |
| BMI (kg/m²)    | 24.8 (22.3–27.0) | 24.7 (22.5–27.3) | 0.435   |
| SBP (mmHg)     | 153 ± 20  | 146 ± 23  | <0.001  |
| DBP (mmHg)     | 92 ± 14   | 89 ± 16   | 0.01    |
| Antihypertensive medication (DDD) | 1.5 (1.0–2.0) | 1.0 (0.2–2.0) | <0.001  |
| Duration of hypertension (years) | 7 (2–13) | 3 (0–8) | <0.001  |
| Diabetes, n (%) | 66 (23.7%) | 124 (27.9%) | 0.226   |
| Preexisting CVD, n (%) | 39 (14.0%) | 48 (10.8%) | 0.198   |
| Target organ damage, n (%) | 88 (31.7%) | 67 (15.1%) | <0.001  |
| History of hypokalemia, n (%) | 206 (74.1%) | 139 (31.2%) | <0.001  |
| Scr (μmol/L) | 71 (58–89) | 88 (57–83) | 0.045   |
| Serum K⁺ (mEq/L) | 3.3 (2.9–3.8) | 3.9 (3.6–4.2) | <0.001  |
| hs-CRP (mg/L) | 1.1 (0.5–2.5) | 1.0 (0.4–2.9) | 0.616   |
| Plasma aldosterone concentration (pg/mL) | 270.0 (192.0–401.0) | 116.0 (72.3–171.0) | <0.001  |
| PRC (μIU/mL) | 2.5 (0.9–7.0) | 12.8 (5.1–32.2) | <0.001  |
| ARR (pg·mL⁻¹/μIU·mL⁻¹) | 100.3 (33.2–319.2) | 7.2 (3.2–21.7) | <0.001  |
| hs-TnT (ng/L) | 7.0 (4.0–12.0) | 6.0 (3.0–11.0) | 0.005   |
| CK-MB (μg/L) | 1.4 (1.0–2.0) | 1.3 (0.9–1.9) | 0.154   |
| Myoglobin (μg/L) | 24.2 (21.0–38.1) | 21.8 (21.0–31.9) | 0.023   |

Data were presented as mean ± SD, %, or median (interquartile range); BMI, body index mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; DDD, defined daily dose; CVD, cardiovascular diseases; Scr, serum creatinine; hs-CRP, high sensitivity C-reactive protein; PRC, plasma renin concentration; ARR, plasma aldosterone/renin ratio; hs-cTnT, high sensitivity troponin T; CK-MB, creatine kinase isoenzyme MB.
TABLE 2 | Univariate linear regression between myocardial injury markers and clinical characteristics in the study participants.

| Characteristics                  | PA (n=278) | Non-PA (n=445) | All the crowd (n=723) |
|----------------------------------|------------|----------------|----------------------|
|                                  | hs-cTnT    | CK-MB          | Myoglobin            | hs-cTnT    | CK-MB          | Myoglobin            | hs-cTnT    | CK-MB          | Myoglobin            |
| Age (years)                      |            |                |                      | β          | β              | β                    | β          | β              | β                    |
| Hb (g/dL)                        | -0.01      | -0.07          | -0.03                | -0.03      | -0.07          | -0.07                | -0.03      | -0.07          | -0.07                |
| Total cholesterol (mg/dL)        | 0.01       | 0.03           | 0.09                 | 0.06       | 0.03           | 0.09                 | 0.06       | 0.03           | 0.09                 |
| BMI (kg/m²)                      | 0.01       | 0.05           | 0.04                 | 0.01       | 0.03           | 0.05                 | 0.01       | 0.03           | 0.05                 |
| Antihypertensive medication (DDD)| -0.01      | -0.07          | -0.09                | -0.01      | -0.07          | -0.09                | -0.01      | -0.07          | -0.09                |
| Duration of hypertension (years) | 0.05       | 0.03           | 0.01                 | 0.09       | 0.03           | 0.01                 | 0.09       | 0.03           | 0.01                 |
| Preexisting CVD                  | -0.03      | -0.07          | -0.09                | -0.01      | -0.07          | -0.09                | -0.01      | -0.07          | -0.09                |
| Target organ damage              | -0.04      | -0.02          | 0.05                 | -0.03      | -0.01          | 0.01                 | -0.03      | -0.01          | 0.01                 |
| Scr (umol/L)                     | -0.02      | -0.01          | 0.01                 | 0.06       | 0.04           | 0.16**               | 0.04       | 0.02           | 0.07                 |
| Serum K+ (mmol/L)                | -0.02      | -0.07          | -0.07                | 0.07       | 0.07           | -0.07                | 0.04       | 0.02           | 0.07                 |
| Plasma aldosterone concentration (pg/mL) | 0.06 | 0.38** | 0.40**               | -0.04 | 0.04 | 0.04               | 0.03 | 0.30** | 0.31**               |
| hs-cTnT/CRP (mg/L)               | -0.02      | 0.00           | 0.12                 | -0.03      | 0.14**         | 0.08                 | -0.02      | 0.04           | 0.09**                |
| hscTnT (ng·L⁻¹)                  | 0.06       | 0.41**         | 0.37**               | 0.01      | 0.01           | 0.01                 | -0.01      | 0.35**         | 0.32**                |

**P < 0.01, *P < 0.05.

**DISCUSSION**

Previous study showed that aldosterone is associated with damages to heart and skeletal muscle cells (16–19), while very few studies have evaluated serum levels of muscle injury markers in PA patients. For the first time, we compared serum levels of hs-TnT, CK-MB and myoglobin between patients with PA and EH. We found that hs-TnT and myoglobin were higher in PA patients than that in EH patients. Univariate linear regression analysis showed that myoglobin is negatively associated with serum potassium and positively associated with plasma aldosterone concentration in PA patients. The relationship existed after adjusting for some potential confounders, especially the serum potassium, blood pressure, DDD, duration of hypertension, the proportion of diabetes, preexisting CVD, and target organ damage and age.

hs-TnT is specific and sensitive biomarkers of myocardial injury. It is the preferred serologic tests for the evaluation of patients with suspected acute myocardial infarction (31–33). In addition to acute myocardial injury, previous studies have found that serum hs-TnT is increased in many chronic diseases, such as chronic heart failure, pulmonary hypertension, stable coronary heart disease, and chronic kidney disease (34, 35). Our study found that hs-TnT increased in PA patients when compared with subjects with EH. However, no significant correlation was found between serum hs-TnT and plasma aldosterone concentration or other clinical parameters, suggesting that hs-TnT elevation in PA patients may be resulted from other underlying factors. In addition to hs-TnT, high sensitivity troponin I (hs-TnI) has also been reported to be associated with nonfatal myocardial infarction (36), whether hs-TnI is superior to hs-TnT for indicating aldosterone induced myocardial injury requires more studies.

Creatine kinase is an important energy-regulating enzyme in muscle tissues that catalysis creatine-generated creatine phosphate and ADP with the energy provided by ATP. Creatine kinase is a dimer comprising two subunits, M and B, and CK-MB mainly exists in the myocardium and skeletal muscle (37). CK-MB are elevated when muscle cells are damaged, which included acute myocardial infarction, myocarditis and myositis (38). However, we did not find higher CK-MB in PA patients than EH in our study. Although there is a correlation between CK-MB and plasma aldosterone concentration, it might have little clinical significance.

Interestingly, our study found myoglobin was increased in PA patients when compared with subjects with EH. In fact, patients with disease which might obviously influence the three markers were excluded from our study. The increase of myoglobin found here in PA patients was not as high as in acute myocardial injury or rhabdomyolysis, and it did not reflect acute muscle injury. Myoglobin is a cytoplasmic hemoprotein that is synthesized in cardiomyocytes and skeletal muscle cells. It is an oxygen storage protein, capable of releasing oxygen during periods of hypoxia or

TABLE 3 | Multivariate linear regression between myocardial injury markers and biochemical characteristics in the study participants.

| Characteristics                  | PA (n=278) | Non-PA (n=445) | All the crowd (n=723) |
|----------------------------------|------------|----------------|----------------------|
|                                  | hs-cTnT    | CK-MB          | Myoglobin            | hs-cTnT    | CK-MB          | Myoglobin            | hs-cTnT    | CK-MB          | Myoglobin            |
| Serum K+ (mmol/L)                | -0.09      | -0.13**        | -0.15*               | 0.04       | -0.09          | -0.05                | 0.01       | -0.11**        | -0.11**               |
| Plasma aldosterone concentration (pg/mL) | 0.02 | 0.32** | 0.34**               | -0.03 | 0.05 | 0.04               | -0.01 | 0.28** | 0.26**               |

*Adjusted for age, sex, BMI, SBP, DBP, DDD, duration of hypertension, diabetes, preexisting CVD, target organ damage, and plasma aldosterone concentration.

**Adjusted for age, sex, BMI, SBP, DBP, DDD, duration of hypertension, diabetes, preexisting CVD, target organ damage, and serum K+.

**P < 0.01, *P < 0.05.
anoxia (39, 40). The serum levels of myoglobin increase in acute and chronic muscle injuries and decrease with age as the muscle mass becomes less in older people (41, 42). In our study, when age, BMI, blood pressure and serum potassium were adjusted, myoglobin is still positively correlated with plasma aldosterone concentration in PA patients. This is a retrospective study, and it is not clear which of the high aldosterone level and the increased myoglobin level observed in the study came first. It has been reported that aldosterone can directly damage skeletal and cardiac muscle cells (16, 18, 19), while aldosterone receptor antagonists can improve the injury of muscle cells (16, 43–46). Although we found that myoglobin was independently associated with plasma aldosterone concentration in PA patients, whether the level of myoglobin might change after mineralocorticoid receptor antagonists (MRA) treatment was not clear. Aldosterone receptors are widely expressed in tissues and cells throughout the body, including cardiac and skeletal muscle cells. There is a possibility that excessive production of aldosterone in the adrenal cortex may directly or indirectly caused myoglobin release in muscle cells. However, the hypothesis needs further study to verify.

Several limitations in this study should be mentioned. First, this is a retrospective study and the comparison of muscle injury markers in EH and PA cohorts might be affected by potential differences in the underlying phenotypes of the two cohorts. However, clinical characteristics including age, sex and BMI were similar between the two cohorts. Second, this is a cross-sectional study, although a positive association was found between plasma aldosterone concentration and myoglobin, causal relationship between them could not be answered by this study. Third, myoglobin exists not only in in cardiac muscles but also in skeletal muscles and which one is the source of the elevated myoglobin in PA patients was not clear. In addition, other indicators of muscle damage and potential confounding factors such as total creatine kinase, magnesium and calcium ions were not detected in this study.

CONCLUSION

The serum level of myoglobin was significantly increased in PA patients, and myoglobin was independently correlated with plasma aldosterone concentration, which might be a reflection of chronic muscle injury in PA patient.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL, F-FW, JH, and SY contributed to conception and design of the study. JH and SY supervised the study. YS, YY, MM, and LM organized the database. BK, KW, and CP performed the statistical analysis. BK and CP wrote the first draft of the manuscript. KW and YY wrote the sections of the manuscript. All authors contributed to article and approved the submitted version.

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