Risk of new-onset dyslipidemia after laparoscopic adrenalectomy in patients with primary aldosteronism

（原発性アルドステロン症に対する腹腔鏡下副腎摘除術後の

脂質代謝異常症新規発症リスク）

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Abstract

Background: Many patients with primary aldosteronism (PA) show a significant decline in kidney function after adrenalectomy. Thus, PA patients who undergo surgery are at greater risk of both postoperative renal damage and new-onset metabolic events associated with renal insufficiency. The aim of this study was to explore postoperative changes in serum lipid levels and to identify risk factors associated with postoperative new-onset dyslipidemia in PA patients.

Methods: The records of 57 Japanese patients who underwent unilateral laparoscopic adrenalectomy for PA were retrospectively surveyed. Clinical and biochemical data were evaluated at baseline and 12 months after surgery. Preoperative and postoperative estimated glomerular filtration (eGFR) and serum lipid profile, including triglycerides, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol levels, were compared. Furthermore, uni- and multivariate analyses were performed to determine the predictors for postoperative new-onset dyslipidemia.

Results: A significant decrease in eGFR and deterioration of serum lipid levels was identified postoperatively in most patients. Of the 39 patients without pre-existing dyslipidemia, 18 developed new-onset dyslipidemia postoperatively. Multivariate analysis identified preoperative lower eGFR and higher body mass index as independent predictors for new-onset dyslipidemia after surgery. On univariate analyses, additional factors associated with new- onset dyslipidemia included older age, male sex, higher LDL-cholesterol, and higher LDL/HDL ratio.

Conclusions: PA patients had a higher risk of postoperative new-onset or progressive dyslipidemia. Clinicians should pay attention to not only follow-up of renal impairment but also total management of new-onset metabolic events associated with renal insufficiency in PA patients.

Introduction

Primary aldosteronism (PA) is caused by the autonomous secretion of aldosterone from adrenocortical lesions, and it is associated with hypertension due to sodium retention [1–3]. Excessive production of aldosterone in patients with PA has been associated with substantial cardiovascular and renal damage [3–7]. Moreover, some studies have reported that aldosterone independently contributes to the development of the cardiometabolic syndrome, including hyperglycemia and dyslipidemia [4, 8].

Adrenalectomy can lead to a significant decrease in the glomerular filtration rate, as a consequence of correcting the glomerular hyperfiltration peculiar to PA [3, 9–14]. Furthermore, it is well known that the progression of renal insufficiency eventually causes cardiometabolic events, such as dyslipidemia and premature atherosclerosis [15–20]. Thus, PA patients who undergo adrenalectomy are at greater risk of both postoperative renal damage and new- onset metabolic events associated with renal insufficiency. So far, there have been no reports on postoperative lipid profile changes in PA patients. The aim of the present study was to explore postoperative changes in serum lipid levels and to identify risk factors associated with new-onset dyslipidemia after adrenalectomy in Japanese PA patients.

Materials and Methods

Medical records at Chiba University Hospital were retrospectively searched from August 1998 to March 2013. Unilateral PA was diagnosed as described before and the underlying adrenocortical lesion was pathologically assessed in all patients after surgery [2, 9, 10]. All patients were cured with postoperative plasma aldosterone concentration (PAC) decreased to <12 ng/dL. Fifty-seven Japanese patients who underwent laparoscopic adrenalectomy for unilateral PA were analyzed in the present study. Patients with incomplete data about serum lipid profiles or follow- up for <12 months were excluded from this study. Eighteen patients had a medical history of dyslipidemia before adrenalectomy and 39 did not. None of these patients had taken any lipid-lowering drugs or had any medical history of primary kidney disease at the time of surgery.

The development of new-onset dyslipidemia or deterioration of serum lipid levels was assessed at 12 months after surgery. Dyslipidemia was defined as hypertriglyceridemia (≥150 mg/dL), hypo-high-density lipoprotein (HDL)-cholesterolemia (<40 mg/dL), and/or hyper-low-density lipoprotein (LDL)-cholesterolemia (≥140 mg/dL) according to Japan Arteriosclerosis Society definitions [21].

The following were collected from medical records: age, sex, body mass index (BMI), duration of hypertension, comorbidities, blood pressure (BP), and clinical laboratory data. These laboratory data included PAC, suppressed plasma renin activity (PRA), serum levels of potassium, HDL-cholesterol, LDL-cholesterol, and triglycerides, the LDL-cholesterol/HDL-cholesterol (LDL/HDL) ratio, and the estimated glomerular filtration rate (eGFR). The eGFR was calculated using a new equation that has

been developed and validated in a Japanese population [22].

The results are reported as medians (range) or as means ± standard deviation, as appropriate. Continuous parametric variables were compared using *t*-tests. Non-parametric variables were compared using Mann-Whitney *U* tests. Categorical variables were compared using χ^2 tests or Fisher's exact test. First, baseline characteristics of patients with/without preoperative dyslipidemia were assessed and compared. Second, the changes of eGFR and serum lipid levels in patients were compared using paired *t*-tests or Wilcoxon signed rank tests. Third, univariate analyses were performed to evaluate the association between new-onset dyslipidemia and preoperative variables. After significant candidate variables were selected based on univariate analyses, multivariate logistic regression analysis was used to identify clinical predictors associated with new-onset dyslipidemia. Significance was defined at the level of $p < 0.05$. All statistical analyses were carried out using IBM SPSS Statistics 22.

Results

Table 1 shows the baseline characteristics of the patients, 18 of the 57 PA patients had a medical history of dyslipidemia preoperatively. The following variables differed significantly in patients with/without preoperative dyslipidemia: medical history of diabetes, PAC, and serum lipid levels. Table 2 shows the postoperative changes of eGFR and serum lipid levels in patients with/without preoperative dyslipidemia. In both groups, eGFR was significantly lower after surgery. Analysis of lipid profiles in 18 patients with preoperative dyslipidemia showed significant increases in LDL-cholesterol (p =0.02) and the LDL/HDL ratio (p <0.01) postoperatively. On the other hand, analysis of lipid profiles in 39 patients without preoperative dyslipidemia showed significant increases in triglycerides (p <0.01), in addition to LDL-cholesterol levels and the LDL/HDL ratio. Table 3 shows postoperative changes of eGFR and serum lipid levels in patients without preoperative dyslipidemia. These patients were divided into two groups according to postoperative eGFR ($\geq$60 and <60 mL/min/1.73 m^2). In the postoperative eGFR <60 mL/min/1.73 m^2 group, HDL-cholesterol significantly decreased (p <0.01) and triglycerides and the LDL/ HDL ratio significantly increased (p <0.01). Meanwhile, in the postoperative eGFR $\geq$60 mL/min/1.73 m^2 group, LDL-cholesterol significantly increased (p =0.03), as did triglycerides (p <0.01).

Of the 39 patients without preoperative dyslipidemia, 18 developed dyslipidemia postoperatively. Preoperative factors associated with new-onset dyslipidemia on uni- and multivariate analyses are summarized in Table 4. On univariate analyses, older age, male sex, higher BMI, lower eGFR, higher

LDL-cholesterol, and a higher LDL/HDL ratio were significantly associated with new-onset dyslipidemia (p <0.05). LDL-cholesterol and the LDL/HDL ratio were excluded from the variables incorporated into the multivariate analysis, because the definition of dyslipidemia was established using serum lipid levels. Thus, the following variables were incorporated into the multivariate analysis: sex, age, BMI, and eGFR. It was found that higher BMI and lower eGFR were independent predictors of new-onset dyslipidemia.

Discussion

Many patients with PA show a significant decline in eGFR postoperatively, because the glomerular hyperfiltration state resolves, as we have described before [9]. Additionally, the progression of postoperative renal insufficiency causes dyslipidemia and premature atherosclerosis [15-20]. Therefore, PA patients who undergo adrenalectomy are at greater risk of both postoperative renal damage and new-onset metabolic events associated with renal insufficiency.

Many studies have shown that chronic kidney disease (CKD) is an important cause of secondary dyslipidemia. Abnormalities of serum lipoprotein composition are present in nearly all patients with mild to severe renal disease, even those with normal serum lipid levels [15-18]. Generally, the serum triglyceride concentration starts to increase with a mild decrease of kidney function [23], while the serum HDL-cholesterol concentration is consistently decreased in patients with CKD [15-17, 19]. However, the serum LDL-cholesterol concentration tends to remain near normal in patients with CKD, but the serum levels of LDL-cholesterol may rise in CKD patients with proteinuria [15-17, 19].

In the present study, both patients with postoperative eGFR <60 and those with postoperative eGFR ≥60 mL/min/1.73 m^2 showed a significant decrease in eGFR after adrenalectomy. Moreover, patients with postoperative eGFR <60 mL/min/1.73 m^2 showed a significant increase in triglycerides and a significant decrease in HDL-cholesterol, whereas patients with postoperative eGFR ≥60 mL/min/1.73 m^2 showed a significant increase in triglycerides, but they did not show a significant decrease in HDL-cholesterol (Table3). The present novel findings suggest that postoperative renal damage could cause

the increase of triglycerides and the decrease of HDL-cholesterol. Unfortunately, there is no obvious explanation for why LDL-cholesterol significantly after surgery, because proteinuria could not be assessed in this retrospective study.

Although HDL-cholesterol did not show a significant decrease in both patients with/without preoperative dyslipidemia, there were significant increases of triglycerides and LDL-cholesterol, and there was a tendency towards decreased HDL (Table 2). This study is the first to show that serum lipid levels were postoperatively aggravated in PA patients.

The LDL/HDL ratio has been considered to be a clinically useful marker, because dyslipidemia with an increased LDL and decreased HDL predisposes to atherogenesis. Hence, an increased LDL/HDL ratio is associated with an increased risk of cardiovascular event, baseline LDL/HDL ratios above 2.5 are associated with an especially increased cardiovascular event risk [24, 25]. Tables 2 and 3 show that the LDL/HDL ratio significantly increased and was above 2.5, except in patients with postoperative eGFR $\geq$60 mL/min/1.73 m^2. These findings suggest that the abnormality of postoperative serum lipid levels might cause progressive atherosclerosis in PA patients.

In the present study, clinical predictors for new-onset dyslipidemia after adrenalectomy in PA patients were identified first (Table 4). Lower eGFR (p <0.02) and higher BMI (p =0.01) were significantly associated with postoperative new-onset dyslipidemia. Renal damage and obesity can strongly affect progressive dyslipidemia [19]. These simple clinical factors can be used widely, so clinicians are able to pay attention to patients at greater risk of dyslipidemia and decide on suitable

early interventions for dyslipidemia.

The present study has some limitations. The retrospective nature of the study might have affected the quality of the data. First, missing data such as consecutive serum lipid profiles and proteinuria could not be evaluated. Thus, this small cohort study was finally conducted in 57 patients. Second, this study with a follow-up of 12 months might have been too short to assess renal failure and dyslipidemia in PA patients. Although the present study represents the first report of the effects of surgical management of PA on the development of dyslipidemia, further study is needed to corroborate these findings and to further clarify these associations.

In conclusion, PA patients had a higher risk of new-onset or progressive dyslipidemia after laparoscopic adrenalectomy. Clinicians should pay attention to not only follow-up of renal impairment, but also comprehensive management of new-onset metabolic events associated with renal insufficiency in PA patients.

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Table 1. Baseline characteristics of patients with primary aldosteronism

Variable	With preoperative dyslipidemia (N=18)	Without preoperative dyslipidemia (N=39)	*p*
Age, years	54.0 (45.0-72.0)	54.0 (23.0-73.0)	0.26
Male, n (%)	8 (44.4)	20 (51.3)	0.63
BMI (kg/m^2)	24.4 (±3.4)	22.9 (±3.1)	0.12
Duration of hypertension, years	7.0 (1.0-27.0)	10.0 (0.0-30.0)	0.49
Comorbidities			
Cardiovascular disease, n (%)	1 (5.6)	8 (20.5)	0.15
Cerebrovascular disease, n (%)	3 (16.7)	3 (7.7)	0.28
Diabetes mellitus, n (%)	6 (33.3)	4 (10.3)	0.04
Systolic BP (mmHg)	147.2 (±24.5)	152.4 (±23.9)	0.46
Diastolic BP (mmHg)	93.5 (±16.1)	90.6 (±16.8)	0.54
PAC (ng/dL)	28.8 (±27.3)	40.3(±30.6)	0.02
PRA (ng/mL/h)	0.1 (0.0-1.0)	0.2 (0.0-4.1)	0.57
Potassium (mmol/L)	3.0 (±0.5)	3.1 (±0.7)	0.58

eGFR (mL/min/1.73 m^2)	73.7 (±16.3)	80.3 (±21.6)	0.26
HDL-cholesterol (mg/dL)	49.8 (±13.5)	63.4 (±18.5)	<0.01
LDL-cholesterol (mg/dL)	134.1 (±21.9)	109.9 (±20.6)	<0.01
Triglycerides (mg/dL)	164.4 (±65.3)	83.0 (±24.2)	<0.01
LDL/HDL ratio	2.8 (±0.7)	1.9 (±0.6)	<0.01

BMI, body mass index; BP, blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. Postoperative changes of serum lipid levels in patients with primary aldosteronism

Variable	Before surgery	After surgery	*p*
With preoperative dyslipidemia (N=18)			
eGFR (mL/min/1.73 m^2)	73.7 (±16.3)	59.8 (±15.4)	<0.01
HDL-cholesterol(mg/dL)	49.8 (±13.5)	45.6 (±13.0)	0.16
LDL-cholesterol(mg/dL)	134.1 (±21.9)	144.6 (±23.8)	0.02
Triglycerides (mg/dL)	164.4 (±65.3)	209.0 (±82.3)	0.05
LDL/HDL ratio	2.8 (±0.7)	3.4 (±1.3)	<0.01
Without preoperative dyslipidemia (N=39)			
eGFR (mL/min/1.73 m^2)	80.3 (±21.6)	64.4 (±17.4)	<0.01
HDL-cholesterol(mg/dL)	63.4 (±18.5)	60.4 (±20.5)	0.15
LDL-cholesterol(mg/dL)	109.9 (±20.6)	119.7 (±26.3)	<0.01
Triglycerides (mg/dL)	83.0 (±24.2)	136.8 (±70.2)	<0.01
LDL/HDL ratio	1.9 (±0.6)	2.3 (±1.0)	<0.01
New-onset dyslipidemia in patients without preoperative dyslipidemia (N=18)			
eGFR (mL/min/1.73 m^2)	65.6 (±12.8)	50.6 (±8.3)	<0.01
HDL-cholesterol(mg/dL)	62.5 (±23.1)	57.6 (±25.3)	0.15
LDL-cholesterol(mg/dL)	115.7 (±15.7)	128.4 (±26.1)	<0.01
Triglycerides (mg/dL)	81.7 (±23.9)	158.3 (±94.2)	<0.01

LDL/HDL ratio	2.2 (±0.6)	3.0 (±0.9)	<0.01

eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 3. Postoperative changes of serum lipid levels in patients without preoperative dyslipidemia

Variables	Before surgery	After surgery	*p*
Postoperative eGFR <60 (N=14)			
eGFR (mL/min/1.73 m^2)	63.1 (±16.3)	46.8 (±11.0)	<0.01
HDL-cholesterol(mg/dL)	61.4 (±20.8)	52.2 (±25.6)	<0.01
LDL-cholesterol(mg/dL)	119.8 (±11.2)	133.8 (±26.4)	0.06
Triglycerides (mg/dL)	89.6 (±27.8)	171.9 (±82.6)	<0.01
LDL/HDL ratio	2.1 (±0.6)	3.0 (±1.0)	<0.01
Postoperative eGFR ≥60 (N=25)			
eGFR (mL/min/1.73 m^2)	89.9 (±18.0)	74.3 (±11.3)	<0.01
HDL-cholesterol(mg/dL)	64.5 (±17.5)	65.0 (±15.7)	0.69
LDL-cholesterol(mg/dL)	104.3 (±22.7)	111.9 (±23.3)	0.03
Triglycerides (mg/dL)	79.4 (±21.7)	117.2 (±54.7)	<0.01
LDL/HDL ratio	1.8 (±0.6)	1.8 (±0.7)	0.26

eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 4. Uni- and multivariate analyses of preoperative variables for new-onset dyslipidemia in patients with primary aldosteronism

Preoperative variables	Univariate			Multivariate	
	New-onset dyslipidemia (n=18)	Non new-onset dyslipidemia (n=21)	*p*	Odds ratio (95% CI)	*p*
Age (years)	67.1 (±4.6)	59.7 (±1.5)	0.03	-	0.44
Male, n (%)	13 (72.2)	6 (28.6)	<0.01	-	0.32
BMI (kg/m^2)	26.2 (18.9-27.0)	23.2 (19.2-23.8)	<0.01	1.11-2.33	0.01
Duration of hypertension (years)	19.5 (1.50-30.0)	10.0 (10.0-17.0)	0.06		
Comorbidities					
Cardiovascular disease, n (%)	3 (16.7)	5 (23.8)	0.70		
Cerebrovascular disease, n (%)	1 (5.5)	2 (9.5)	1.00		
Diabetes mellitus, n (%)	3 (16.7)	1 (4.7)	0.32		
Systolic BP (mmHg)	147.2 (±29.8)	157.7 (±24.6)	0.94		
Diastolic BP (mmHg)	79.8 (±16.0)	76.3 (±13.1)	0.26		
PAC (ng/dL)	31.6 (11.6-48.2)	31.3 (24.0-31.5)	0.28		
PRA (ng/mL/h)	0.2 (±0.1)	0.2 (±0.2)	0.17		
Potassium, (mmol/L)	3.5 (±0.7)	3.0 (±0.4)	0.10		
eGFR (mL/min/1.73 m^2)	60.8 (42.6-81.3)	69.4 (69.4-81.1)	<0.01	0.86-0.97	<0.01
HDL-cholesterol (mg/dL)	54.3 (±14.8)	63.0 (±22.9)	0.07		
LDL-cholesterol (mg/dL)	120.5 (±7.7)	101.7 (±22.5)	<0.01	-	-
Triglycerides (mg/dL)	89.3 (±27.8)	73.3 (±11.9)	0.17		
LDL/HDL ratio	2.2 (±0.6)	1.6 (±0.5)	<0.01	-	-

BMI, body mass index; BP, blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; CI, confidence interval.

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