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Transtubular potassium gradient predicts kidney function impairment after adrenalectomy in primary aldosteronism

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Abstract

Background: In primary aldosteronism (PA), kidney function impairment could be concealed by relative hyperfiltration and emerge after adrenalectomy. We hypothesized transtubular gradient potassium gradient (TTKG), a kidney aldosterone bioactivity indicator, could correlate to end organ damage and forecast kidney function impairment after adrenalectomy.

Methods: In the present prospective study, we enrolled lateralized PA patients who underwent adrenalectomy and were followed up 12 months after operation in the Taiwan Primary Aldosteronism Investigation (TAIPAI) registry from 2010 to 2018. The clinical outcome was kidney function impairment, defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 at 12 months after adrenalectomy. End organ damage is determined by microalbuminuria and left ventricular mass.

Results: In total, 323 patients [mean, 50.8 ± 10.9 years old; female 178 (55.1%)] were enrolled. Comparing pre-operation and post-operation data, systolic blood pressure, serum aldosterone, urinary albumin to creatinine ratio and eGFR decreased. TTKG $\geqslant 4.9$ correlated with pre-operative urinary albumin to creatinine ratio >50 mg/g [odds ratio (OR) = 2.42; $p = 0.034$] and left ventricular mass (B = 20.10; $p = 0.018$). Multivariate logistic regression analysis demonstrated that TTKG $\geqslant 4.9$ could predict concealed chronic kidney disease (OR = 5.42; $p = 0.011$) and clinical success (OR = 2.90, $p = 0.017$) at 12 months after adrenalectomy.

Conclusions: TTKG could predict concealed kidney function impairment and cure of hypertension in PA patients after adrenalectomy. TTKG more than 4.9 as an adverse surrogate of aldosterone and hypokalaemia correlated with pre-operative end organ damage in terms of high proteinuria and cardiac hypertrophy.

Keywords: adrenalectomy, kidney function impairment, primary aldosteronism, transtubular potassium gradient

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Introduction

Primary aldosteronism (PA) is the most common cause of secondary hypertension.[1] Related to persistent hypertension and volume retention,[2] PA patients have high incidence of end organ damage[3,4] and cardiovascular events[5] when compared with essential hypertension patients. In aldosterone producing adenoma (APA), refractory hypertension could be correctable when patients receive adrenalectomy.[6]

In addition to high blood pressure that damages kidney structure,[7,8] aldosterone directly contributes to injury to the kidneys *via* the genomic and non-genomic pathway.[9] In rodent studies, aldosterone infusion induced glomerular, kidney vascular injury[10] and interstitial fibrosis.[11] Furthermore, longstanding aldosterone excess accelerates hyperfiltration in the kidneys.[12] Kidney hyperfiltration contributes to early renal damage in pre-diabetes and pre-hypertension patients.[13] Related to

enhanced sodium reabsorption by excess aldosterone, kidney hyperfiltration in PA[12,14] is more significant and will augment kidney damage together with the presence of abnormal urinary albumin excretion.[4,15] However, relative kidney hyperfiltration masks deteriorating kidney function[12,16] and makes kidney function impairment difficult to isolate. Therefore, kidney function impairment may be concealed in PA patients and emerge after adrenalectomy.

Low serum potassium was reported to predict declined estimated glomerular filtration rate after adrenalectomy in PA patients.[17] Potassium secretion in the kidney cortical collecting duct is mainly modulated by aldosterone.[18] PA patients may have refractory hypokalaemia related to persistent aldosterone stimulation in kidney. Transtubular potassium gradient (TTKG), a formula to gauge renal potassium secretion by the cortical collecting duct,[19,20] had been used as bioactivity marker of aldosterone on kidney.[20,21] The aim of the present study was to investigate whether TTKG could predict kidney function impairment after surgical treatment in PA patients and its relationship with end organ injury.

Methods

Ethics statement

The study complied with the Declaration of Helsinki and was approved by the National Taiwan University Hospital Research Ethics Committee (No. 200611031R). All participants received comprehensive written information and signed a consent form before inclusion in the study.

Patients' selection

The present study is a cohort study enrolling PA patients from 2010 to 2018 who received adrenalectomy and were followed up to 12 months with serum creatinine data. The individuals were registered in the Taiwan Primary Aldosteronism Investigation (TAIPAI) database.[22–31] The study group included two medical centres (National Taiwan University Hospital (NTUH), Taipei, Taiwan; Taipei University Hospital, Taipei, Taiwan) and five regional hospitals (Cardinal Tien Hospital, New Taipei City, Taiwan; Taipei Tzu Chi Hospital, New Taipei City, Taiwan; Yun- Lin Branch of NTUH, Douliou City, Taiwan; Hsin-Chu Branch of NTUH, Hsin-Chu City, Taiwan; Zhongxing Branch of Taipei City Hospital, Taipei, Taiwan).[32]

All antihypertensive medications were discontinued for at least 21 days before confirmation tests. Doxazosin and/or diltiazem were administered to control markedly high blood pressure when required.[25]

The diagnosis of PA in hypertensive patients was based on the following criteria:

Confirmation. Fulfilment of the following three conditions confirmed a diagnosis of PA:[28,31]

(a) Autonomous excess aldosterone production evidenced with a 24-h urinary aldosterone level (Uald-24 h) more than 20.3 μg; (b) a TAIPAI score larger than 60%;[26] (c) Seated post-saline loading plasma aldosterone concentration (PAC) >16 ng/dl or PAC/plasma renin activity (PRA > 35 (ng/dl)/(ng/ml/h) shown in a post-captopril test.

The probability of PA (TAIPAI score)[26] was equal to: $= 1/1 + e^{-}\beta$, where $\beta = [PAC\ (ng/dl) \times (0.063)] + [PRA\ (ng/ml/h) \times (-0.205)] + [(ARR \times 0.001) + BMI(kg/m^2)\ x\ (0.067)] + [Male \times (-0.738) + Serum\ potassium(mmol/L) \times (-1.512)] + [eGFR(ml/min/1.73\ m^2) \times (0.017)] + [(propensity\ score) \times (-0.539) + (1.851)]$, where ARR represents aldosterone-renin ratio, BMI represents body mass index and eGFR represents estimated glomerular filtration rate.

The propensity score was described as our previous report.[26]

Functional survey. The aldosterone concentration was measured by radioimmunoassay using a commercial kit (Aldosterone Maia Kit, Adaltis Italia S.P.A., Bologna, Italy)[33] and PRA was measured by the generation of angiotensin I *in vitro* using a commercially available radioimmunoassay kit (DiaSorin, Stillwater, MN, USA).[34]

Lateralization and subtype identification. APA is identified on the basis of PA patients following:[31] (a) lateralization of aldosterone secretion at adrenal venous sampling (AVS) or during dexamethasone suppressing NP-59 SPECT/CT[35] and confirm adrenal adenoma in hematoxylin and eosin (HE) stain; or (b) pathologically proven

adenoma after an adrenalectomy and stained with positive CYP11B2 stain.[28]

Clinical parameters and assessment of outcome

General information about age, sex, body weight, BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. We collected biochemistry data about serum creatinine, potassium and osmolality, and urine creatinine, potassium, albumin and osmolality. The estimated glomerular filtration rate was calculated *via* the Chronic Kidney Disease Epidemiology Collaboration formula. Transtubular potassium gradient was calculated by using the formula: urine K/plasma K ÷ urine osmolality/plasma osmolality. Cardiac echo was conducted before surgical treatment. All echocardiography[36] was performed using a Hewlett-Packard 5500 ultrasound system with an S3 transducer (1.0–3.0 MHz). Two-dimensional, M-mode, Doppler and tissue Doppler ultrasonography were performed in each patient, and the dimensions of the chamber, wall thickness and left ventricular ejection fraction (M-mode) were measured according to the guidelines of the American Society of Echocardiography.[37]

An eGFR of less than 60 ml/min/1.73 m^2 was defined as kidney function impairment.[7,38,39] Since declining eGFR became steady 6–12 months after adrenalectomy was reported,[7,16,40] we assessed post-operative eGFR at 12 months after adrenalectomy as the primary endpoint.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequency and percentage. Paired *t*-test and Chi-squared test were used to distinguish the differences prior to and after surgical treatment. An independent *t*-test was applied to distinguish variables between different groups. Pearson correlation test and multivariate linear regression analysis were carried out to evaluate the relationship between interested variables. Covariates were age, sex, body weight, BMI, SBP, DBP, log aldosterone values, PRA, ARR, pre-operation eGFR, serum potassium levels and TTKG value. In order to depict the implications of TTKG for individual patients, a generalized additive model (GAM) incorporating the subject-specific (longitudinal) random effects were plotted and adjusted with other parameters to predict the possibility of outcome.[30,41] The optimal cut-off value was defined as the log odd equalling zero.[31] After finding the optimal cut-off value of TTKG, univariate and multivariate logistic regression analyses were applied to evaluate TTKG and other covariates relative to the clinical outcome and end organ damage. Binary logistic regression analysis with a stepwise variable selection procedure was adopted using available variables to identify the important factors associated with post-operative complete clinical success. The significance levels for entry and for stay were conservatively set at 0.15.

Statistical significance was defined as two-sided p value < 0.05. Statistical analyses were performed with IBM SPSS statistics version 17 (Armonk, NY: IBM Corp) software and R software. All analyses were performed with R software, version 3.2.2 (Free Software Foundation, Inc., Boston, MA).[42]

Results

Clinical characteristic prior to and after 12 months of adrenalectomy

The present study enrolled 341 patients of unilateral PA patients who underwent adrenalectomy and were followed up to 12 months after the operation. Although eGFR was supposed to decline due to relief of hyperfiltration after adrenalectomy, we could not exclude the possibility that improved blood pressure had beneficial effects on renal function recovery. We observed that some individuals who had pre-operative eGFR less than 60 ml/min/1.73 m^2, which we defined as renal function impairment, could recover after adrenalectomy. But none of the individuals who had pre-operative eGFR less than 45 ml/min/1.73 m^2 recovered to above eGFR 60ml/min/1.73 m^2. Thus, we excluded the 18 individuals with an eGFR less than 45 ml/min/1.73 m^2 at the baseline.[43] Finally, 323 enrolees were included for analysis. Included participants possessed a mean age of 50.8 ± 10.9 years and were 44.9% male. Comparing values before and 12 months after the operation, there were significant improvements in SBP, DBP, plasma aldosterone levels, PRA, ARR, serum potassium levels and urine albumin to creatinine ratio (ACR); however, eGFR was decreased (Table 1).

Table 1. Characteristics of study cohort in primary aldosteronism patients before and 12 months of adrenalectomy.

Variables	Before adrenalectomy	12 months after adrenalectomy	*p* value
No of participants	323	323	
Age (years)	50.8 ± 10.9	NA	
Sex, Female (%)	178 (55.1%)	NA	
Body weight (kg)	68.5 ± 14.3	NA	
Body mass index (kg/m^2)	25.6 ± 4.0	NA	
ACEI or ARB	143 (44.1%)	62 (19.1%)	<0.001
α-blocker	77 (23.8%)	12 (3.7%)	0.014
β-blocker	139 (42.9%)	50 (15.4%)	<0.001
CCB	225 (69.4%)	87 (26.9%)	0.022
Vasodilator	18 (5.6%)	9 (2.8%)	0.027
Diuretics	36 (11.1%)	8 (2.5%)	<0.001
Hypertension duration (years)	7.6 ± 7.0	NA	
SBP (mm Hg)	154.6 ± 21.3	135.0 ± 17.7	<0.001
DBP (mm Hg)	92.8 ± 13.9	83.9 ± 11.5	<0.001
Plasma aldosterone level (ng/dl)	60.4 ± 40.9	31.0 ± 19.6	<0.001
Plasma renin activity (ng/ml/hr)	0.72 ± 2.80	3.34 ± 6.73	<0.001
Aldosterone renin ratio	1358 ± 2807	122 ± 596	<0.001
Serum creatinine level (mg/dl)	0.89 ± 0.25	1.06 ± 0.84	<0.001
eGFR (EPI-Cr, ml/min/1.73 m^2)	88.8 ± 19.7	78.9 ± 22.3	<0.001
Kidney function impairment	37 (11.5%)	70 (21.7%)	<0.001
Serum potassium level (mEq/L)	3.5 ± 0.7	4.3 ± 0.4	<0.001
Urine albumin over creatinine ratio (mg/g)	86 ± 22	32 ± 96	0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI-Cr, Epidemiology Collaboration creatinine equation; NA, not available; SBP, systolic blood pressure; TTKG, transtubular potassium gradient.

TTKG predicted kidney function impairment 1 year after adrenalectomy in PA patients

To find the adequate cut-point value of pre-operative TTKG that predicted kidney function impairment at 12 months after adrenalectomy, a GAM plot was plotted. At the cut point of 4.9, higher TTKG forecasted an eGFR less than 60 ml/min/1.73 m^2 at 1 year after surgical treatment (Figure 1). In full adjusted multivariate logistic regression analysis, systolic blood pressure [odds ratio (OR) = 1.06; 95% confidence interval (CI), 1.02–1.11; $p = 0.002$], pre-operative eGFR (OR = 0.91; 95% CI, 0.87–0.95; $p < 0.001$) and TTKG ≥ 4.9 (OR = 5.42; 95% CI, 1.48–19.85; $p = 0.011$) were independent predictors of kidney function impairment (Table 2). Further assessment was conducted to evaluate confounding of anti-hypertension drugs (Supplemental Table S1).

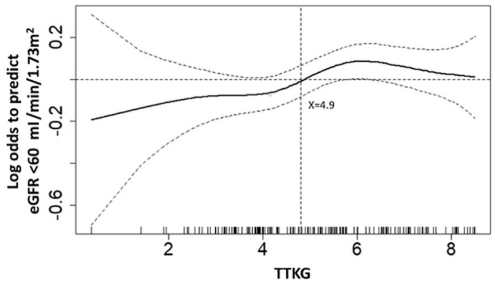

Figure 1. GAM plot for TTKG and eGFR < 60 ml/min/1.73 m². GAM plot for the probability of TTKG and eGFR < 60 ml/min/1.73 m² after 12 months of adrenalectomy against TTKG of APA patients incorporating the subject-specific (longitudinal) random effects expressed as the logarithm of the odds (logit). The probability of outcome events was constructed with hypertensive duration have an average of zero over the range of the data, that is, TTKG = 4.9. The dashed lines indicate approximated pointwise 95% CI. Dotted curves indicate 95% CIs for the smoothed hazard.
APA, aldosterone producing adenoma; ARR, aldosterone to renin ratio; BMI, body mass index; BW, body weight; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GAM, generalized additive model; PRA, plasma renin activity; SBP, systolic blood pressure; TTKG, transtubular potassium gradient.

Baseline factors associated with TTKG

Pearson correlation test demonstrated that TTKG correlated with pre-operative log aldosterone values ($r = 0.30$; $p < 0.001$) and serum potassium levels ($r = -0.39$; $p < 0.001$). Pre-operative log aldosterone values (OR = 5.93; 95% CI, 1.56–22.50; $p = 0.009$) and serum potassium levels (OR = 0.33; 95% CI, 0.19–0.59, $p < 0.001$) were associated with TTKG ⩾ 4.9 by logistic regression analysis (Supplemental Table S2). When comparing between TTKG ⩾ 4.9 and TTKG < 4.9 individuals (Supplemental Table S3), pre-operative aldosterone values (64.83 ± 42.74 *versus* 45.56 ± 24.27; $p < 0.001$) and serum potassium (3.39 ± 0.64 *versus* 3.77 ± 0.56; $p < 0.001$) were significantly different. In comparison with TTKG < 4.9 individuals (Supplemental Table S3), TTKG ⩾ 4.9 individuals were more influenced by adrenalectomy. TTKG ⩾ 4.9 individuals had a higher difference of eGFR[12] before and after adrenalectomy and a significant decline of urinary ACR[12] by the time of operation (Figure 2).

Table 2. Baseline characteristics predicting eGFR < 60 ml/min/1.73 m² after 12 months of adrenalectomy by logistic regression analysis.

	Univariable		Multivariable	
	Odds ratio (95% CI)	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age (year)	1.06 (1.03–1.09)	<0.001		
Gender (Male)	0.34 (0.19–0.58)	<0.001		
Body weight (kg)	1.02 (1.01–1.04)	0.012		
BMI (kg/m²)	1.07 (1.01–1.15)	0.032		
SBP (mmHg)	1.04 (1.02–1.05)	<0.001	1.06 (1.02–1.11)	0.002
DBP (mmHg)	1.02 (1.00–1.04)	0.014		
eGFR (EPI-Cr, ml/min/1.73m²)	0.93 (0.91–0.94)	<0.001	0.91 (0.87–0.95)	<0.001
Log aldosterone	4.27 (1.55–11.81)	0.005		
Plasma renin activity (ng/ml/hr)	1.26 (1.02–1.55)	0.031		
Log aldosterone renin ratio	0.52 (0.32–0.84)	0.007		
Potassium (mEq/L)	0.66 (0.44–1.00)	0.049		
TTKG ⩾ 4.9	2.10 (0.97–4.53)	0.059	5.42 (1.48–19.85)	0.011

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI-Cr, Epidemiology Collaboration creatinine equation; SBP, systolic blood pressure; TTKG, transtubular potassium gradient.

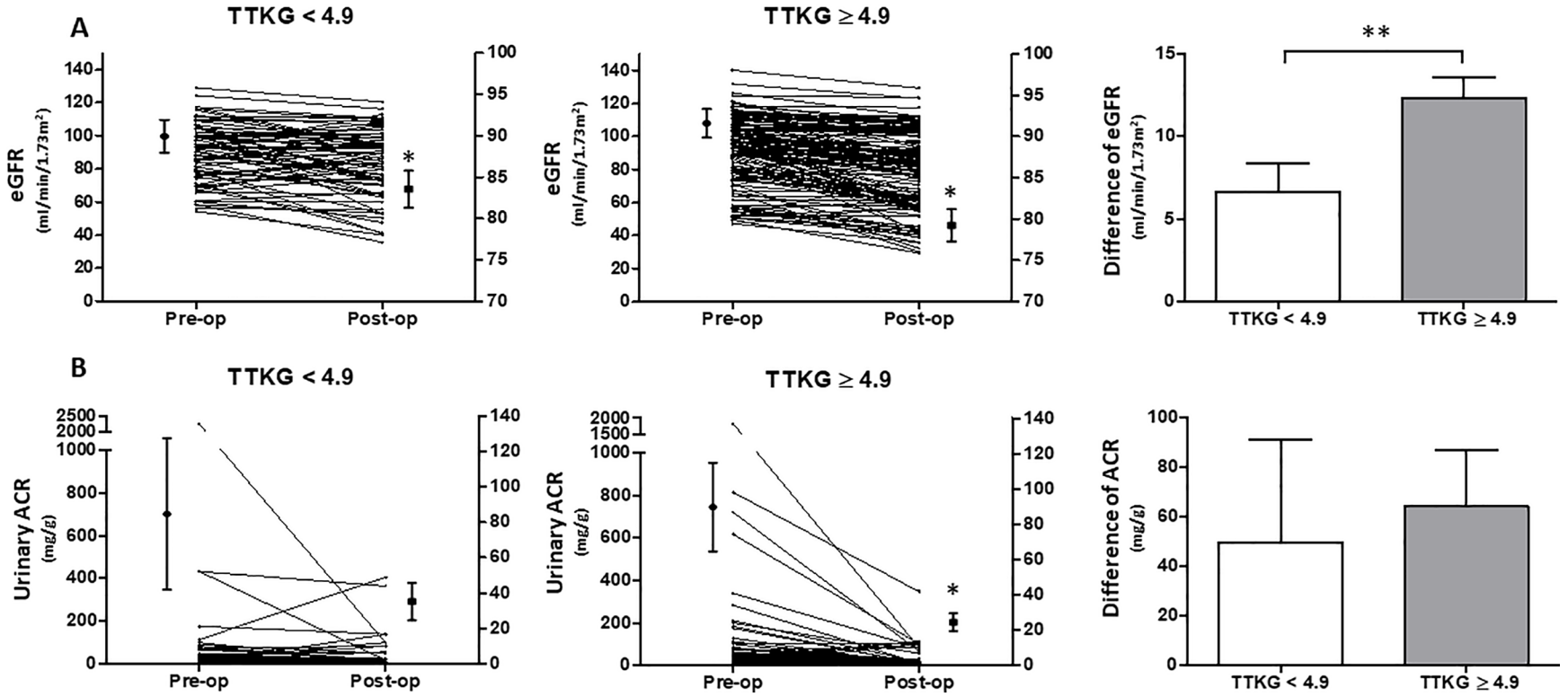

Figure 2. The eGFR and urinary ACR before and after adrenalectomy in TTKG < 4.9 or TTKG ≥ 4.9 groups. The patients were categorized into TTKG < 4.9 or TTKG ≥ 4.9 groups. The eGFR and urinary ACR were more influenced by adrenalectomy in TTKG ≥ 4.9 group. (A) After operation, the eGFR in both groups decreased significantly (*). However, the difference of eGFR before and after adrenalectomy was more significant in TTKG ≥ 4.9 group *versus* TTKG < 4.9 group (**). (B) The urinary ACR dropped more remarkably in patients with TTKG ≥ 4.9 after adrenalectomy, whereas TTKG < 4.9 patients did not have significant decline of urinary ACR. Left Y axis indicates the values of variables. Right Y axis indicates the values of mean ± SEM.

*p represented < 0.05 and statistical analysis was conducted by compare t-test.

**p represented < 0.05 and statistical analysis was conducted by independent t-test.

eGFR, estimated glomerular filtration; TTKG, transtubular potassium gradient; Urinary ACR, urinary albumin to creatinine ratio.

Table 3. The association between pre-operation variables predicting LV mass by linear regression analysis.

	Univariable		Multivariable	
	B Coefficient	***p* value**	**B Coefficient**	***p* value**
Age (year)	−0.593	0.137		
Gender (Male)	−65.93	<0.001	−29.21	0.018
Body weight (kg)	2.46	<0.001	1.79	0.029
BMI (kg/m^2)	6.12	<0.001		
SBP (mmHg)	1.11	<0.001	0.78	0.005
DBP (mmHg)	1.47	<0.001		
eGFR (EPI-Cr, ml/min/1.73 m^2)	−0.54	0.016		
Log aldosterone	38.97	0.026	33.58	0.033
Plasma renin activity (ng/ml/hr)	3.17	0.251		
Log aldosterone renin ratio	−7.45	0.311		
Potassium (mEq/L)	−17.49	0.010		
TTKG ⩾ 4.9	9.46	0.381	20.10	0.018

The multivariate regression analysis was conducted by full adjustment of variables.
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI-Cr, Epidemiology Collaboration creatinine equation; LV, left ventricle; SBP, systolic blood pressure; TTKG, transtubular potassium gradient.

In addition to the binominal definition of kidney function impairment, we further tested the percentage change of eGFR before and after adrenalectomy. TTKG ⩾ 4.9 also was associated with percentage decrease of eGFR (Supplemental Table S4) and predicted a 20% decrease of eGFR after adrenalectomy (OR = 2.55; 95% CI, 1.11–5.88, $p = 0.028$) (Supplemental Table S5).

Sensitivity analysis

TTKG was originally to be applied when urine osmolality is more than serum osmolality.[44] We further excluded patients who had urine osmolality less than serum osmolality ($n = 167$). In light of our main result, TTKG could constantly predict kidney function impairment (OR = 5.57; 95% CI, 1.22–25.35; $p = 0.026$) by full adjustment of variables.

Furthermore, we excluded individuals with a pre-operative eGFR of less than 60 ml/min/1.73 m^2 ($n = 183$).[16,40,45] TTKG ⩾ 4.9 could constantly forecast kidney function impairment at 1 year of adrenalectomy (OR = 5.05; 95% CI, 1.31–19.48; $p = 0.019$).

Diabetic mellitus (DM) interferes with endothelium dysfunction and might affect the prediction of TTKG. Therefore, we attempted to exclude diabetic patients for analysis. In non-DM patients ($n = 182$), TTKG ⩾ 4.9 correlates with kidney impairment after adrenalectomy (OR = 3.43; 95% CI, 1.17–10.07; $p = 0.025$).

Since hypertension could promote kidney impairment,[46] while increased body mass index would be a risk factor for impaired kidney function,[47] we further applied subgroup analysis by categorizing patients into SBP > 140 or ⩽140 mmHg and BMI ⩾ 25 or <25 (kg/m^2). In patients with pre-operative hypertension (OR = 3.51; 95% CI, 1.36–9.01; p = 0.009), and in patients with increased BMI (OR = 3.39; 95% CI, 1.12–10.33; $p = 0.031$), TTKG ⩾ 4.9 could predict kidney function impairment after adrenalectomy.

Table 4. Pre-operation characteristics predicting urinary ACR > 50 mg/g by logistic regression analysis.

	Univariable		Multivariable (Backward conditional)	
	Odds ratio (95% CI)	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age (year)	1.00 (0.98–1.02)	0.838		
Gender (Male)	0.90 (0.54–1.51)	0.699		
Body weight (kg)	1.01 (0.99–1.03)	0.258		
BMI (kg/m^2)	1.08 (1.01–1.15)	0.016	1.11 (1.01–1.21)	0.027
SBP (mmHg)	1.02 (1.01–1.04)	<0.001	1.02 (1.00–1.04)	0.045
DBP (mmHg)	1.04 (1.02–1.06)	<0.001		
eGFR (EPI-Cr, ml/min/1.73 m^2)	0.99 (0.98–1.01)	0.243		
Log aldosterone	1.21 (0.45–3.23)	0.706		
Plasma renin activity (ng/ml/hr)	1.01 (0.92–1.10)	0.900		
Log aldosterone renin ratio	0.96 (0.63–1.45)	0.832		
Potassium (mEq/L)	0.82 (0.56–1.21)	0.326		
TTKG ⩾ 4.9	2.01 (0.95–4.28)	0.070	2.42 (1.07–5.47)	0.034

The multivariate regression analysis was conducted by full adjustment of variables.
ACR, albumin to creatinine ratio; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPI-Cr, Epidemiology Collaboration creatinine equation; SBP, systolic blood pressure; TTKG, transtubular potassium gradient.

TTKG correlated with end organ injury

With linear regression analysis, females, increased body weight, SBP, log aldosterone level and TTKG ⩾ 4.9 correlated with increased pre-operative left ventricular mass (Table 3). Furthermore, we assessed the relationship of TTKG to proteinuria. TTKG ⩾ 4.9 predicted pre-operative ACR > 50 mg/g (OR = 2.42; 95% CI, 1.07–5.47; $p = 0.034$) (Table 4).

Cure of hypertension after adrenalectomy

We assessed the variables to cure hypertension after adrenalectomy according to the Primary Aldosteronism Surgery Outcome (PASO) consensus. We categorized patients into clinical success groups, in terms of complete success, partial success and absent success groups. TTKG ⩾ 4.9 could predict clinical success after adrenalectomy (OR = 2.90; 95% CI, 1.21–6.92; $p = 0.017$) (Supplemental Table S6).

Discussion

Our findings suggest that TTKG, a marker to gauge renal potassium secretion by the cortical collecting duct in terms of hyperaldosteronism and hypokalaemia, could predict kidney function impairment after adrenalectomy even with a high possibility to cure hypertension. TTKG could correlate to end organ damage such as increased left ventricle (LV) mass, microalbuminuria. The demonstration of enhanced potassium excretion in patients with PA opens new avenues for better understanding the mechanisms of aldosterone-induced kidney dysfunction.

TTKG in PA

PA patients with TTKG ⩾ 4.9 had high aldosterone values and low serum potassium levels. TTKG ⩾ 4.9 individuals were more affected by adrenalectomy since they had higher difference of eGFR and significant urinary ACR decline. The results indicated

that TTKG ≥ 4.9 individuals had higher pre-operative kidney hyperfiltration compared with TTKG < 4.9 individuals. In multiple variate logistic regression analysis, TTKG was independent of serum aldosterone and potassium levels in predicting kidney function impairment after adrenalectomy. This implies that high TTKG patients had higher aldosterone production and mineralocorticoid activity than their counterpart. Potassium excretion in principle cells rely on epithelium sodium channel (ENac) to reabsorb sodium and subsequently trigger potassium efflux from apical (potassium) K^+ channel.[48] Moreover, hyperfiltration relative to sodium retention increases urinary flow rate in the cortical collecting duct and further stimulates potassium secretion.[48] Taken together, inappropriately high TTKG was associated with abnormal ENac activation by hyperaldosterone and low serum potassium levels[49] in our data.

TTKG associate with kidney fibrosis

In patients with hyperaldosteronism, high TTKG reflects adverse activity of aldosterone on kidney fibrosis. In PA patients, the pre-treatment plasma potassium level was reported as an independent risk factor for eGFR decline after treatment.[17]

Long-term stimulation of ENac by aldosterone could increase intracellular sodium concentration in kidney tubular cells. Intracellular overload of sodium subsequently induces intracellular calcium overload[50] and stimulates calcium calmodulin kinase II (CaMKII)[50,51] which is found in human renal tubule cells[52] and modulates ENac activity.[53] CaMKII contributes to aldosterone associated fibrosis in kidney collecting duct cells.[54] Furthermore, colocalization of signals for urinary potassium/urinary creatinine and CaMKIIG was found in genome-wide association studies (GWAS).[55] Sustained high TTKG might be accompanied by persistent high intracellular sodium concentration, urinary potassium excretion and CaMKII activation, and further associated with kidney fibrosis.

TTKG correlates with organ damage

In our analysis, high TTKG was associated with end organ damage with the manifestation of increased LV mass. Inappropriate high TTKG in PA is accompanied with volume expansion and hyperfiltration. High intraglomerular pressure results in podocyte injury and subsequently proteinuria. Inflammation caused by aldosterone[15] contributes to glomerulus damage. In regards to the heart, in addition to direct aldosterone effect, increased renal ENac subunits play a pivotal role in the pathogenesis of chronic heart failure in rodent models.[56] Hypokalaemia in PA also could stimulate CaMKII[50] and further provoke cardiac inflammation[57] and hypertrophy.[58,59]

Furthermore, decreased cardiac pump function eliminates blood supply to the severely oxygen-dependent kidney.[60] Despite whole kidney hyperfiltration in PA and increased GFR, damage to endothelium cells and microstructure in the kidney and accompanied heart dysfunction ultimately results in kidney impairment.

High urinary potassium excretion has been reported to increase the risk of kidney function impairment progression.[61] Hyperfiltration related to sustained ENac activation could induce proteinuria.[62,63] Moreover, genomic colocalization of urinary ACR and urinary potassium/urinary creatinine in glycine amidinotransferase locus was found in GWAS analysis[55] and provided evidence that urinary potassium excretion correlated to albuminuria. This could explain why high TTKG was associated with microalbuminuria in our study, as microalbuminuria reflects systemic vascular endothelium dysfunction.[64] In the long-term follow-up of primary hypertension without DM and other major diseases, baseline microalbuminuria increased the risk of declined renal function.[65] Taken together, we showed that high urine potassium excretion was associated with an increased risk of developing kidney function impairment in PA patients after adrenalectomy at least partially *via* increased proteinuria.[55]

TTKG predicts clinical cure after adrenalectomy

Adrenalectomy decreased blood pressure and urinary albuminuria in our PA patients[7] that could be beneficial to organ injury. However, in the PASO study,[66] the plasma aldosterone levels did not have significant differences between the groups of complete clinical success *versus* absent clinical success, or between partial clinical success *versus* absent clinical success. In our analysis, high TTKG is found to be a predictive factor to clinical success after adrenalectomy according to the PASO criteria.[66] It is possible that TTKG reflects mineralocorticoid bioactivity together with hypokalaemia on the target organ and predicts more accurately the clinical outcome after the correction of aldosterone excess by adrenalectomy.

Study limitation

TTKG is suggested to be operated when urine osmolality is more than serum osmolality.[44] In light of this, we excluded individuals whose urine osmolality was less than serum osmolality, and high TTKG could predict post-operative kidney function impairment.

Baseline kidney function is associated with impaired kidney function after adrenalectomy and could interfere with the evaluation of TTKG. We have found that some patients who have pre-operative eGFR less than 60 ml/min/1.73m^2 were improved after adrenalectomy.[43] Nonetheless, even if we excluded patients who had pre-operative eGFR less than 60 ml/min/1.73m^2, defined as our primary endpoint, TTKG could be associated with post-operative kidney impairment.

Conclusions and implication

In summary, our study strengthens the body of observational literature suggesting that kidney potassium handling and hyperaldosterone, in terms of TTKG, could predict kidney impairment and cure hypertension at 12 months after adrenalectomy in unilateral PA patients. High TTKG was associated with end organ damage; more specifically, it was correlated with LV mass and urinary albumin excretion, even with a high possibility to cure hypertension.

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Author contributions

HWL: acquisition of data, analysis and interpretation of data and wrote the first draft. SMW: interpreted the revised result and provided the methods for statistics. CKC: conceived the review topic, provided additional supplemental results and drafted the revised article. YHL: conceived the review topic, interpreted the response letter and responded with further statistics. PCL: revised and approved the final version of the manuscript and drafted the revised article. CHH: revised and approved the final version of the manuscript and acquired the results. YCL: revised and approved the final version of the manuscript, responded with further statistics and revised it critically for important intellectual content. JSC: critical revision of manuscript for intellectual content. VCW: study concept and design, interpretation of data, critical revision of manuscript for intellectual content and final approval of the version to be published.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, V.C.W. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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Supplemental material

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