Impact of primary aldosteronism on renal function in patients with type 2 diabetes

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ABSTRACT
Aims/Introduction: Renal dysfunction might quickly progress in patients with type 2 diabetes mellitus, when accompanied by hypertension. However, whether primary aldosteronism (PA), which autonomously over-secretes aldosterone, causes additional renal damage in patients with type 2 diabetes mellitus is unclear. We evaluated the impact of PA on renal function in patients with type 2 diabetes mellitus.

Materials and Methods: A retrospective review of all patients with type 2 diabetes mellitus who visited Yokohama Rosai Hospital’s outpatient department between April 2017 and March 2018 was carried out. Records of patients with PA who underwent PA treatment by adrenalectomy or mineralocorticoid receptor antagonists (PA group) and those without PA (non-PA group) were extracted, and renal function was compared between the two groups. Untreated PA patients were excluded, as their renal function might be overestimated as a result of glomerular hyperfiltration.

Results: There were 83 patients in the PA group and 1,580 patients in the non-PA group. The PA group had significantly lower estimated glomerular filtration rates than the non-PA group (66.3 [52.4–78.2] vs 70.5 [56.0–85.6] mL/min/1.73 m², P = 0.047). Multiple regression analysis showed that PA was a factor for decreased estimated glomerular filtration rate, independent of age, sex, glycated hemoglobin, diuretic use and hypertension (P = 0.025). PA induced a 3.7-mL/min/1.73 m² (95% confidence interval 0.47–6.9) decrease in estimated glomerular filtration rate, equivalent to that induced by 4.4 years of aging.

Conclusions: Our results show that in patients with type 2 diabetes mellitus, PA is an independent risk factor for renal dysfunction. To prevent the progression of renal failure, PA should not be overlooked.

INTRODUCTION
In recent years, there has been a steady increase in the number of patients with type 2 diabetes mellitus. Diabetic kidney disease is a typical complication of type 2 diabetes mellitus, and is an important cause of end-stage renal disease requiring renal replacement therapy1. As renal dysfunction in patients with type 2 diabetes mellitus will easily progress, especially when accompanied by hypertension2, blood pressure control is a crucial step in the management of type 2 diabetes mellitus. Primary aldosteronism (PA) is one of the most important causes of secondary hypertension, accounting for 5–10% of all patients with hypertension3. PA is associated with lower estimated glomerular filtration rates (eGFR) and higher urine albumin-to-creatinine ratio (UACR) than essential hypertension (eHT)4,5. Previous studies have highlighted the role of the renin–angiotensin–aldosterone system in renal dysfunction in patients with type 2 diabetes mellitus6,7; however, it is still unclear whether PA, which results in autonomous oversecretion of aldosterone, causes additional renal damage in type 2 diabetes mellitus patients. Two previous cross-sectional studies showed that renal function did not differ between type 2 diabetes mellitus patients with PA and without PA5,8. However, care should be taken when interpreting these results. First, the limited number of study participants might be associated with low statistical power. Additionally, in these studies, most patients with PA were evaluated before treatment by adrenalectomy or mineralocorticoid receptor antagonists (MRAs). As eGFR in PA patients decreases after treatment, possibly as a result of release from glomerular hyperfiltration9–11, the actual
renal function in these patients should be evaluated after treatment by adrenalectomy or MRAs.

Therefore, the aim of the present study was to investigate the influence of PA on renal function in patients with type 2 diabetes mellitus by comparing renal function between type 2 diabetes mellitus patients with PA after treatment by surgery or MRAs and those without PA, in a relatively larger population than in previous studies.

**METHODS**

**Research design**

We carried out a retrospective, cross-sectional study using patients’ electronic medical records (EMR) system from Yokohama Rosai Hospital. Informed consent was obtained in the form of opt-out on the website of Yokohama Rosai Hospital, as there were no interventions or further examinations. This study was carried out in accordance with the recommendations of the Declaration of Helsinki, and was approved by the research ethics committee of Yokohama Rosai Hospital (Approval No. 30–35).

**Patient selection and data collection**

A retrospective review of the EMR of all outpatients who visited our hospital, a high-volume center for patients with PA (~600 patients with PA visit our center each year)\(^{12}\), between April 2017 and March 2018 was carried out. In our EMR system, we could extract only coded or structured data automatically without checking the medical records of each patient. Coded or structured data included patients’ profiles, disease names, examination findings (e.g., eGFR, UACR and glycated hemoglobin [HbA1c]), physical data (height, weight and body mass index [BMI]) and drug prescriptions. Disease names were searched by using the International Classification of Diseases, Tenth Revisions (ICD-10) codes. Unstructured data including information described in the narrative free text, such as blood pressure, disease duration and smoking/drinking habits, were not able to be extracted automatically in our system. Because we analyzed a large number of patients, and some data described in the free text were missing and thought to be unreliable, we analyzed only coded or structured data in the whole analysis.

Meanwhile, we manually checked pretreatment status for PA in all patients with PA to carry out further analysis. We confirmed the EMR of each patient with PA to extract information described in the text, including age at the time of diagnosis of hypertension, age at the start of PA treatment and some examination findings, which were unable to be extracted automatically.

We extracted data of patients with type 2 diabetes mellitus, and then divided these patients into two groups – patients with PA who underwent PA treatment (PA group) and patients without PA (non-PA group). We compared renal function between these two groups and examined factors that affected renal function.

Patients with type 2 diabetes mellitus were defined as patients who had the following diseases "type 2 diabetes (ICD-10 codes: E11–") or "diabetes mellitus (ICD-10 codes: E14–") and who had HbA1c ≥6.5% or were being treated with antidiabetic agents. Patients with the disease names "type 1 diabetes (ICD-10 codes: E10–),“ gestational diabetes (ICD-10 codes: O24–) or disease names associated with specific types of diabetes (ICD-10 codes: E12– and E13–), were excluded\(^{13}\).

Patients with PA were defined as patients who had the disease name ‘PA (ICD-10 code: E26.0)’ and who underwent PA treatment. Treatment for PA was defined as adrenalectomy or the use of MRAs, as these were the treatments recommended by the Endocrine Society Clinical Guideline\(^{3}\). In the PA group, we ensured that all patients met one or more positive confirmatory test for PA\(^{3,14,15}\). Patients with untreated PA with the disease name "PA" but who did not undergo PA treatment were excluded, as renal damage might be underestimated in these patients. In addition, patients with the disease names “Cushing’s syndrome (ICD-10 codes: E24–),“ “pheochromocytoma (ICD-10 code: D35.0),” “renal cell carcinoma (ICD-10 code: C64),” “glomerulonephritis (ICD-10 codes: N03– or N05–)” or those with eGFR <15 mL/min/1.73 m\(^2\) were also excluded.

Patients with hypertension were defined as those who had the disease name “hypertension (ICD-10 code: I10),” whereas dyslipidemia patients were defined as those who had the disease names “dyslipidemia (ICD-10 code: E78.5),” “hypercholesterolemia (ICD-10 code: E78.0)” or “hypertriglyceridemia (ICD-10 code: E78.1).”

The daily dose of some antihypertensive drugs (MRA, angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin II receptor blocker [ARB] and diuretics [thiazide or loop]) was calculated according to the standard of the defined daily dose (DDD) recommended by the World Health Organization\(^{16}\). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, and it provides a fixed unit of measurement independent of price and dosage form, which enables the researchers to assess and compare drug consumption\(^{16}\).

If examination findings were evaluated twice or more during the research period, only initial findings were analyzed.

**Measurements**

Between February 2007 and January 2016, plasma aldosterone concentration was measured using a radioimmunoassay (SPAC-S Aldosterone Kit; FUJIREBIO Inc.; Tokyo, Japan), whereas from February 2016 onwards, it was measured using a chemiluminescence enzyme immunoassay (Accurease; FUJI-FILM Wako Pure Chemical Corporation, Tokyo, Japan). Plasma renin activities were measured using an enzyme immunoassay (Renin Activity Kit YAMASA; YAMASA Corporation, Chiba, Japan). Urinary albumin was measured using a turbidimetric immunoassay (N-Assay TIA Micro Alb Nittobo; Nittobo Medical Corporation, Tokyo, Japan).
**Statistical analysis**
All statistical analyses were carried out using JMP® software (version 12; SAS Institute Inc., Cary, NC, USA). The Shapiro–Wilk test was carried out to assess the normal distribution of quantitative variables. Data are given as the median (25–75th percentile) or mean ± the standard deviation. The Wilcoxon rank-sum test was used to compare parameters in the PA group with those in the non-PA group. The Wilcoxon signed-rank test was used to compare paired parameters. Relative populations of categorical variables were assessed using the Fisher’s exact test. Predictive factors for decreased eGFR were assessed using single or multiple regression analysis. Multiple regression analyses were carried out using a least squares analysis of variance to clarify the independent factors associated with eGFR. In multiple regression analysis for eGFR, we included age, sex, BMI, HbA1c, hypertension, dyslipidemia, MRA use, ACE-I or ARB use and diuretic (thiazide or loop) use as explanatory variables other than PA, as these parameters have been reported to be associated with renal function17–23.

**RESULTS**

**Patient derivation**
Between April 2017 and March 2018, the EMR of 6,821 patients who visited the outpatient department of the Endocrinology and Diabetes Center at Yokohama Rosai Hospital were extracted for analysis. Of these, 2,028 patients had type 2 diabetes mellitus, with the disease names “type 2 diabetes” or “diabetes mellitus” and HbA1c ≥6.5% or treatment with antidiabetic agents. After excluding 365 patients who met the exclusion criteria, 1,663 patients were further divided into the PA group (n = 83) or the non-PA group (n = 1,580; Figure 1).

**Evaluation of renal function**
In terms of renal function, patients in the PA group had a significantly lower eGFR than those in the non-PA group (66.3 mL/min/1.73 m² [52.4–78.2 mL/min/1.73 m²] vs 70.5 mL/min/1.73 m² [56.0–85.6 mL/min/1.73 m²], P = 0.047). Additionally, UACR was significantly lower in the PA group.

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**Figure 1** | Patient derivation. eGFR, estimated glomerular filtration rate; PA, primary aldosteronism; T2DM, type 2 diabetes.
than in the non-PA group (9.3 mg/gCr [5.3–30.7 mg/gCr] vs 17.3 mg/gCr [6.7–55.9 mg/gCr], $P = 0.040$; Figure 2).

Multiple regression analysis showed that PA was an explanatory factor for decreased eGFR, independent from age, sex, HbA1c, diuretic use and hypertension ($P = 0.025$; Table 2). PA induced a 3.7-mL/min/1.73 m$^2$ (95% confidence interval 0.47–6.9) decrease in eGFR, equivalent to approximately 4.4 years of aging. Multiple regression analysis for eGFR using DDD instead of use of MRA, ACE-I or ARB and diuretic showed a similar result (Table S2). We also carried out a multiple regression analysis after excluding patients without hypertension from the non-PA group. This analysis also showed that PA was an independent explanatory factor for decreased eGFR (Table S3).

**Evaluation of renal function pre- and post-treatment in the PA group**

We carried out further analysis to evaluate the effect of PA treatment on eGFR in the PA group. We extracted pretreatment clinical data by manually confirming the EMR individually, and created a dataset of “PA group at pretreatment” by replacing clinical data in the PA group with data at pretreatment. The duration from PA treatment to eGFR measurement at post-treatment was 5 years (3–10 years).

In the PA group, eGFR and UACR decreased significantly after PA treatment (72 mL/min/1.73 m$^2$ [64.9–88.2 mL/min/1.73 m$^2$] to 66.3 mL/min/1.73 m$^2$ [52.4–78.2 mL/min/1.73 m$^2$], $P < 0.001$, and 14.7 mg/gCr [7.5–61.7 mg/gCr] to 9.3 mg/gCr [5.3–30.7 mg/gCr], $P < 0.001$, respectively; Figure 3). We found no significant differences in eGFR and UACR between patients in the PA group at pretreatment and patients in the non-PA group (72 mL/min/1.73 m$^2$ [64.9–88.2 mL/min/1.73 m$^2$] vs 70.5 mL/min/1.73 m$^2$ [56.0–85.6 mL/min/1.73 m$^2$], $P = 0.069$, and 14.7 mg/gCr [7.5–61.7 mg/gCr] vs 17.3 mg/gCr [6.7–55.9 mg/gCr], $P = 0.790$, respectively; Figure S1). Furthermore, at pretreatment, PA was not an explanatory factor for decreased eGFR in multiple regression analysis ($P = 0.892$; Table S4). We found that eGFR after PA treatment had

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**Table 1 | Comparison of clinical characteristics between patients in the primary aldosteronism group and the non-primary aldosteronism group**

|                      | PA group (n = 83)$^\dagger$ | non-PA group (n = 1,580)$^\ddagger$ | $P$-value |
|----------------------|----------------------------|-------------------------------------|-----------|
| Sex (male/female)    | 43/40                      | 1,032/548                           | 0.014     |
| Age (years)          | 62 [55–69]                 | 66 [55–75]                          | 0.005     |
| BMI (kg/m$^2$)       | 25.9 [23.8–27.8]           | 24.8 [21.7–28.1]                    | 0.019     |
| HbA1c (%)            | 6.8 [6.5–7.1]              | 7.3 [6.7–8.0]                       | <0.001    |
| Hypertension         | 83 (100%)                  | 1,201 (76.0%)                       | <0.001    |
| Dyslipidemia         | 68 (81.9%)                 | 1,277 (80.8%)                       | 0.887     |
| Antihypertensive medication use |                  |                                      |           |
| MRA                  | 63 (75.9%)                 | 36 (2.3%)                           | <0.001    |
| ACE-I or ARB         | 17 (20.5%)                 | 595 (37.7%)                         | 0.002     |
| Calcium channel blocker | 60 (72.3%)              | 451 (28.5%)                         | <0.001    |
| Diuretic (thiazide or loop) | 2 (2.4%)                 | 108 (6.8%)                          | 0.169     |
| β-Blocker            | 2 (2.4%)                   | 48 (3.0%)                           | 1.000     |
| Other$^\S$          | 4 (4.8%)                   | 39 (2.5%)                           | 0.164     |
| Antidiabetic medication use |                    |                                      |           |
| Metformin            | 37 (44.6%)                 | 837 (53.0%)                         | 0.144     |
| Sulfonylurea         | 2 (2.4%)                   | 212 (13.4%)                         | 0.001     |
| Thiazolidinedione    | 2 (2.4%)                   | 200 (12.7%)                         | 0.003     |
| DPP-4 inhibitor      | 43 (51.8%)                 | 919 (58.2%)                         | 0.257     |
| SGLT-2 inhibitor     | 22 (26.5%)                 | 329 (20.8%)                         | 0.216     |
| α-Glucosidase inhibitor | 13 (15.7%)               | 427 (27.0%)                         | 0.021     |
| Glinide              | 13 (15.7%)                 | 287 (18.2%)                         | 0.661     |
| GLP-1 agonist        | 5 (6.0%)                   | 155 (9.8%)                          | 0.339     |
| Insulin              | 3 (3.61%)                  | 357 (22.6%)                         | <0.001    |
| Antidyslipidemic medication use |                  |                                      |           |
| Statin               | 45 (54.2%)                 | 708 (44.8%)                         | 0.113     |
| Ezetimibe            | 8 (9.6%)                   | 69 (4.4%)                           | 0.052     |
| Fibrate             | 5 (6.0%)                   | 62 (3.9%)                           | 0.380     |

Data are reported as the median [interquartile range] or number (percentage). $^\dagger$The primary aldosteronism (PA) group included patients who received PA treatment. $^\ddagger$The non-PA group included patients without PA. $^\S$Other antihypertensive medication included α-blockers, methyldopa and direct renin inhibitors. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; MRA, mineralocorticoid receptor antagonists; PA, primary aldosteronism; SGLT-2, sodium–glucose cotransporter 2.
negative correlations with the time from diagnosis of hypertension to the start of PA treatment (Figure 4).

When we divided patients in the PA group into two subgroups — those treated by adrenalectomy and those treated by MRAs — there were no significant differences between the two groups in eGFR after PA treatment and change in eGFR before and after PA treatment (Table S5).

**DISCUSSION**

The present study showed that eGFR was lower in type 2 diabetes mellitus patients with PA than in those without PA. In addition, we found that PA was an explanatory predictor for decreased eGFR. We also found that eGFR decreased significantly after PA treatment, and there was no difference in eGFR between the PA group at pretreatment and the non-PA group when clinical data in the PA group were replaced with those at pretreatment.

Although we examined the association between renal function and PA in patients with type 2 diabetes mellitus, and showed that eGFR is lower in type 2 diabetes mellitus patients with PA, there are few reports that examined the association between renal function and PA in patients with type 2 diabetes mellitus. Murase et al. investigated the clinical characteristics of the Japanese population with type 2 diabetes mellitus and...
PA, and reported no significant difference in renal function between type 2 diabetes mellitus patients with and without PA. Reincke et al. also examined risk factors for renal dysfunction in patients with PA and those with eHT, and found no significant difference in renal function between type 2 diabetes mellitus patients with PA and those with eHT. Thus, there seems to be no difference in renal function between type 2 diabetes mellitus patients with and without PA when referring to these reports. However, it should be noted that renal function in PA patients in these reports was evaluated without intervention. In general, eGFR and UACR in patients with PA decreases after treatment for PA, possibly as a result of release from glomerular hyperfiltration. Actually, a significant decrease in eGFR and UACR after treatment for PA was observed in the present study (Figure 3), although we should consider the effect of aging for eGFR decline. Therefore, renal function in PA patients in these previous reports might be overestimated. In the present study, renal function in all PA patients was evaluated after treatment by adrenalectomy or MRAs. By this adjustment, we found that eGFR and UACR were lower in patients with type 2 diabetes mellitus with PA than in those without PA. Interestingly, we also found no differences in eGFR between the PA group at pretreatment and the non-PA group when we replaced clinical data in the PA group with pretreatment data. This result shows that when using pretreatment data, renal function in patients with PA looks no different from that in non-PA patients, which is consistent with the results from previous reports. When evaluating renal function in patients with PA, special consideration should be given to whether clinical data are assessed pre- or post-treatment.

We also showed that PA is a predictor of decreased eGFR, independent from hypertension in patients with type 2 diabetes mellitus. In type 2 diabetes mellitus, multiple factors, such as hyperglycemia, hypertension and dyslipidemia, might cause renal damage. The activation of the renin-angiotensin-aldosterone system, in particular, plays a major role in the development of renal dysfunction in patients with type 2 diabetes mellitus and hypertension. Meanwhile, aldosterone excess is thought to cause renal damage in addition to high blood pressure by sodium–water reabsorption. Additionally, some
clinical reports showed that urinary protein was suppressed by administration of MRAs independent from blood pressure change\textsuperscript{24,25}, supporting the blood pressure-independent effect of aldosterone on renal damage. However, although some reports showed that PA patients had lower eGFR than patients with eHT\textsuperscript{4,5}, no study has shown that PA is an independent factor from hypertension for decreased eGFR in patients with type 2 diabetes mellitus. The present results suggest that excess aldosterone by PA causes further renal damage in patients with type 2 diabetes mellitus and hypertension, in whom activation of the renin–angiotensin–aldosterone system might have already occurred\textsuperscript{6}. Analysis for the relationship between aldosterone level and renal damage might clarify more accurate pathophysiology; however, this analysis was hardly possible in the present study, because there were a lot of missing values on renin–aldosterone during the observation period and many patients used antihypertensive medication that affect renin–aldosterone levels.

Recent reports showed the high prevalence of diabetes mellitus in patients with PA\textsuperscript{26,27}. Multiple metabolic influences of PA, including impaired insulin secretion\textsuperscript{28}, increased insulin resistance\textsuperscript{29} and cortisol co-secretion, might cause impaired glucose metabolism\textsuperscript{30}. Although the prevalence of PA among patients with type 2 diabetes mellitus is relatively low\textsuperscript{31}, blood pressure control might be challenging in patients with PA and type 2 diabetes mellitus\textsuperscript{32}. Furthermore, the prevalence of diabetic kidney disease without typical manifestations, such as long-term diabetes, retinopathy, albuminuria and a gradual decrease in eGFR, has recently increased, along with an increase in the prevalence of type 2 diabetes mellitus\textsuperscript{33,34}, and PA can be one of the causes of diabetic kidney disease lacking typical manifestations. Thus, care should be taken in assessing whether hypertension is caused by PA when examining patients with type 2 diabetes mellitus that have high blood pressure. Interestingly, eGFR after PA treatment had a negative correlation with the time from diagnosis of hypertension to the start of PA treatment in the present study (Figure 4). Given this result and previous reports showing that the duration of hypertension was a risk for cardiovascular events in patients with PA\textsuperscript{35,36}, a decline in eGFR might be suppressed by earlier screening and intervention for PA in type 2 diabetes mellitus patients with PA. However, more detailed analysis including a prospective study will be required to clarify the exact relationship, as the correlation showed in the present study was weak.

There were some limitations of the present study. First, as this research was carried out using the EMR and by extracting patient data using disease names, it is unclear whether the diagnostic criteria of PA and type 2 diabetes mellitus were accurately met. In particular, we cannot deny the possibility that some patients with hypertension in the non-PA group might have had PA, although we normally examine the screening test for PA in patients with hypertension according to the Japanese Endocrine Society guideline\textsuperscript{37}. In addition, diabetes in some patients with PA might be affected by endocrinological abnormalities and should be classified as secondary diabetes\textsuperscript{38}. However, we believe that the impact of endocrinological abnormalities on glucose metabolism was not large, as all patients in the PA group were treated by surgery or MRAs. Second, we were unable to extract unstructured data including information described in free text, such as blood pressure, disease duration and smoking/drinking habits, automatically because of our EMR system. Prospective analysis with a unified evaluation method for such information will be required to provide more accurate insights to renal dysfunction in type 2 diabetes mellitus patients with PA. Third, the present study shows the association between PA and renal function in patients with type 2 diabetes mellitus, but the causal relationship and the progress of renal function in the time series are unknown because of the characteristics of a cross-sectional study design. Evaluation of renal function over time after treatment of PA in patients with type 2 diabetes mellitus is an issue that warrants further study. To conclude, in patients with type 2 diabetes mellitus, PA is an independent risk factor for renal dysfunction. To prevent the progression of renal failure, PA should not be overlooked, and should be promptly diagnosed and treated.

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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Defined daily dose of antihypertensive medication between patients in the primary aldosteronism group and the non-primary aldosteronism group.

Table S2 | Multiple regression analysis of estimated glomerular filtration rate levels in all patients using defined daily dose of mineralocorticoid receptor antagonist, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and diuretic.

Table S3 | Multiple regression analysis of estimated glomerular filtration rate levels in all patients with hypertension.

Table S4 | Multiple regression analysis of estimated glomerular filtration rate levels in all patients where clinical data of the primary aldosteronism group are at pretreatment.

Table S5 | Comparison of clinical characteristics and data between patients treated by adrenalectomy and those treated by mineralocorticoid receptor antagonists in the primary aldosteronism group.

Figure S1 | Comparison of estimated glomerular filtration rate and albumin-to-creatinine ratio levels between the primary aldosteronism group at pre-treatment and the non-primary aldosteronism group.