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Aldosterone-to-Renin Ratio Is Associated with Diabetic Nephropathy in Type 2 Diabetic Patients: A Single-Center Retrospective Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: It is well established that primary aldosteronism (PA) and aldosterone-to-renin ratio (ARR) are associated with kidney disease. The aim of this study was to retrospectively investigate the relationship between ARR, urinary albumin excretion (UAE), and estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes from a single center.

Material/Methods: We included 70 patients with type 2 diabetes, UAE ≤100 mg/day, not taking renin-aldosterone system inhibitors, did not meet the diagnostic criteria for PA, and had an ARR <20. The patients were divided into 3 groups: the normal low (NL) group (33 patients) with a UAE <10 mg/day, the normal (N) group (22 patients) with a UAE of 10-29 mg/day, and the microalbuminuria (M) group (15 patients) with a UAE of 30-100 mg/day. The ARR, plasma renin activity (PRA), and plasma aldosterone (PAC) were compared among groups.

Results: The ARR was highest in group M (10.1±4.6), 6.5±0.3 in group NL, and 7.0±2.7 in group N. The PRA and PAC were significantly lower in group M ($P<0.001$). The ARR showed a significant positive correlation with log UAE (r=0.37, $P<0.001$) and a significant negative correlation with eGFR (r=-0.33, $P<0.01$).

Conclusions: High levels of aldosterone relative to renin, which did not fulfill confirmatory criteria for PA, may be one of the risk factors for the development of diabetic nephropathy in patients with diabetes. The present results are supported by previous research showing that an increased ARR without PA was a risk factor for kidney disease.

Keywords: Glomerular Filtration Rate • Diabetes Mellitus, Type 2 • Diabetic Nephropathies • Aldosterone • Renin • Albuminuria

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Background

Diabetic nephropathy is the main cause of end-stage renal failure [1,2] and is diagnosed by increased albuminuria and decreased glomerular filtration rate (GFR) [3]. Multiple factors contribute to diabetic nephropathy, including hyperglycemia, hypertension, and lipid abnormalities [4,5]. The renin-angiotensin-aldosterone system (RAAS) is also well established as one of its factors, and RAAS activity is known to cause vasoconstriction, elevated blood pressure, and increased sodium reabsorption, leading to progressive renal damage [6,7]. Primary aldosteronism (PA) is an endocrine disorder that leads to hypertension and is characterized by low plasma renin activity (PRA) and high plasma aldosterone (PAC) and is reported to account for 10% of hypertensive patients [8,9]. The aldosterone-to-renin ratio (ARR) is widely used as its screening test [7,8]. Patients with PA are thought to be more prone to cerebrovascular and cardiovascular events and organ damage, including brain, heart, and renal damage [9]. Aldosterone promotes sodium (Na) reabsorption via the mineral corticoid receptor (MR) on renal tubular epithelial cells, resulting in increased fluid volume and blood pressure, which is closely related to proteinuria and the development of renal damage [10,11]. MR is present not only on renal tubular epithelial cells but also on vascular endothelial cells and mesangial cells, and is known to induce vascular damage by a mechanism independent of elevated pressure [10,11].

Screening for PA involves a PRA of less than 1 ng/ml/hr and a PAC of 12 ng/dl or more as indicators, and if the ARR (the ratio of PAC to PRA) is 20 or more, then PA is suspected and a more detailed examination is recommended [7,8]. A high ARR is used in screening, as it indicates that PAC is high relative to PRA and also indicates that PRA is suppressed due to the high PAC [7].

Previous research demonstrated that ARR and the level of PAC were inversely associated with GFR in the general population [12,13]. Therefore, the present study investigated the relationship between ARR, urinary albumin excretion (UAE), and GFR in patients with type 2 diabetes mellitus whose ARR was less than 20 and who did not fulfill confirmatory criteria for PA. This retrospective study was conducted at a single center.

Material and Methods

Ethics Statement

This study was conducted according to the Declaration of Helsinki and was approved by our Institutional Review Board (Saiseikai Yokohamashi Tobu Hospital Ethics Committee; approved on July 7, 2021, Approval No. 20210057). In addition, the purpose and content of the study were fully explained in writing to the participants and their voluntary consent was obtained before the study was conducted.

Study Design

We conducted a single-center, retrospective study of the medical records of patients with type 2 diabetes admitted to Saiseikai Yokohamashi Tobu Hospital for glycemic control from 2010 to 2018. The following patients were included in the search criteria: (1) Patients who were not taking RAAS inhibitors such as angiotensin receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACE-I) or diuretics at the time of admission, (2) Patients whose average UAE of urine collection test performed twice after admission was not more than 100 mg/day, and (3) Patients whose PAC and PRA are measured after 30 min of rest and lying down on the day after admission. Patients with a PAC less than 20 ng/dl, PRA less than 10 ng/ml/hr, and an ARR less than 20 who had blood drawn under the above conditions were included in this study. Patients with abnormal hematuria and urinary sediment, urinary tract infection, suspected renal damage other than diabetic nephropathy, serum creatinine (s-Cr) of 1.1 mg/dl or higher, and/or a fasting blood glucose of 300 mg/dl or higher were excluded.

Subjects

A total 70 patients (51 males and 19 females) met these criteria and had a mean age of 53.3±11.0 years, body mass index (BMI) of 22.5±4.0 kg/m^2, and a mean duration of diabetes mellitus of 7.1±6.1 years. Diabetes mellitus was treated with diet only in 5 cases, oral hypoglycemic agents in 29 cases, insulin therapy in 36 cases, and insulin therapy and oral hypoglycemic agents combined in 15 cases. The mean systolic blood pressure was 115.3±24.1 mmHg and the diastolic blood pressure was 75.0±12.2 mmHg. There was a history of hypertension in 21 patients (30%), of which 7 were being treated with antihypertensive medication (6 calcium channel blockers and 1 beta-blockers). The mean UAE in a 24-h urine collection, performed twice, was 22.7±22.5 mg/day, and the estimated glomerular filtration rate (eGFR) was 86.9±21.8 ml/min/1.73 m^2.

The PRA of the subjects was 1.83±1.06 ng/ml/hr, PAC 11.18±3.43 ng/dl, and ARR 7.60±3.74 (**Table 1**). The 70 patients were classified into 3 groups according to the mean values of UAE in the 24-h urine collection performed on the second and third days of hospitalization. There were 33 patients in the normal low group (NL group) with a UAE <10 mg/day, 22 patients in the normal group (N group) with a UAE of 10-29 mg/day, and 15 patients in the microalbuminuria group (M group) with a UAE of 30-100 mg/day.

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Table 1. Clinical characteristics of the patients studied.

SEX (Male/Female)	51/19
Age (years)	53.3±11.0
BMI (kg/m^2)	25.5±4.0
Diabetic duration (years)	7.1±6.1
Diabetic treatment: Insulin/OHA/Diet alone	36/29/5
HbA1c (%)	9.9±1.9
Systolic BP (mmHg)	115.3±24.1
Diastolic BP (mmHg)	75.0±12.2
Hypertension (%)	30
Use of CCB (%)	8.6
LDL-cholesterol (mg/dl)	118.2±37.1
Triglyceride (mg/dl)	219.8±352.0
Serum creatinine (mg/dl)	0.68±0.18
eGFR (ml/min/1.73 m^2)	86.9±21.8
Albuminuria (mg/day)	22.7±22.5
PRA (ng/ml/hr)	1.83±1.06
Plasma aldpsterone (ng/dl)	11.18±3.43
ARR	7.60±3.74

OHA – oral hypoglycemic agents; BP – blood pressure; CCB – calcium channel blocker; eGFR – estimated glomerular filtration rate; PRA – plasma renin activity; ARR – aldosterone/renin ratio. Values are mean±SD.

Measurements

The eGFR was used as an index of renal function tests, and was estimated using the following equation by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2)=194×serum creatinine $^{-1.094}$×age$^{-0.287}$×0.739 (if female) [14]. The RIA method was used to measure plasma renin activity (renin IRMA[FR] kit, Fujirebio, Japan) and plasma aldosterone concentration (Spac-s aldosterone kit, Fujirebio, Japan). At the time of UAE measurement, the absence of urinary tract infection was confirmed by urine sediment and measured by immunoturbidimetry.

Statistical Analysis

Results are expressed as mean±SD. Numerical data were compared between groups using the unpaired *t* tests, and Welch's *t* test was used for analysis if equal variances were not assumed. Pearson's correlation coefficient was used for correlation analyses. In this study, two-sided $P<0.05$ was considered significant. All statistical analyses were performed with SAS JMP version 11 (SAS Institute, Inc. Cary, NC, USA).

Results

Comparison of the Clinical Features of the 3 Groups (Table 2)

Age and BMI were not significantly different among the 3 groups, but the duration of diabetes mellitus was significantly longer in group M. Systolic blood pressure was significantly higher in group M. In contrast, diastolic blood pressure was not significantly different among the 3 groups. HbA1c and eGFR were not significantly different among the 3 groups.

Table 2. Comparison of clinical features of the 3 groups.

	NL group N=33	N group N=22	M group N=15	P<
Age (years)	52.2±10.2	51.9±11.5	58.0±10.8	NS
BMI (kg/m^2)	25.0±2.6	26.3±5.1	25.3±4.4	NS
DM duration (years)	5.4±5.4	6.9±5.0	11.3±7.2	NL vs M 0.0017 N vs M 0.0259
HbA1c (%)	10.2±2.1	9.9±1.6	9.3±1.5	NS
Systolic BP (mmHg)	107.8±20.7	121.0±27.5	123.5±20.7	NL vs M 0.00366 NL vs N 0.04665
Diastolic BP (mmHg)	74.5±12.7	74.0±9.1	77.7±13.9	NS
eGFR (ml/min/1.73 m^2)	95.8±16.7	94.8±25.5	86.2±29.0	NS

NL group – normal low group; N group – normal group; M group – microalbuminuria group; DM – diabetes mellitus; BP – blood pressure; eGFR – estimated glomerular filtration rate; NS – not significant. Values are mean±SD.

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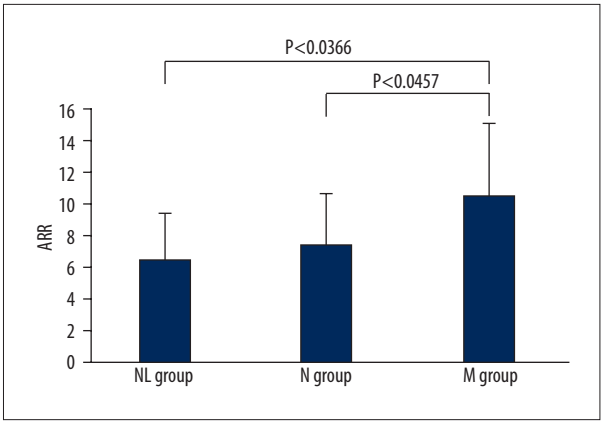

Figure 1. Comparison of aldosterone-to-renin ratio (ARR) among the 3 groups (Paint Shop Pro, Corel Corporation). NL group – normal low group; N group – normal group; M group – microalbuminuria group; ARR – aldosterone/renin ratio. Values are mean±SD.

Comparison of ARR Among the 3 Groups (Figure 1)

ARR was highest in group M (NL group 6.5±0.3, N group 7.0±2.7, M group 10.1±4.6) (NL vs M group *P*<0.0366, N vs M group *P*<0.0457). PRA was the lowest in group M (NL group 2.08±1.13, N group 2.00±1.01, M group 1.05±0.46 ng/ml/hr) (NL vs M group *P*<0.0014, N vs M group *P*<0.00056). Finally, PAC was lowest in group M: 11.27±3.14 in NL group, 12.15±3.37 in N group, and 9.54±3.76 ng/dl in M group (N group vs M group *P*<0.00228).

Correlation of ARR with UAE and eGFR (Figure 2)

ARR showed a significant positive correlation with log-transformed UAE (log UAE) (r=0.36695, *P*<0.0018) and a significant negative correlation with eGFR (r=-0.32595, *P*<0.0063). ARR also showed a significant positive correlation with duration of diabetes (r=0.278071, *P*<0.0198), but had no significant correlation with blood pressure, HbA1c, age, and lipids.

PRA showed a significant negative correlation with log UAE (r=-0.33958, *P*<0.0040), a significant positive correlation with eGFR (r=0.351136, *P*<0.0031), and a significant negative correlation with systolic blood pressure (r=-0.25654, *P*<0.0321). However, PAC did not show a significant correlation with log UAE, eGFR, and blood pressure.

Discussion

This study showed that the ARR was highest in group M, and PRA and PAC were significantly lower in group M compared with group NL and group N. The ARR showed a significant positive correlation with log UAE and a significant negative correlation with eGFR. These findings are supported by previous research showing that ARR and the level of PAC were inversely associated with GFR in the general population [12,13]. Furthermore, a previous study reported that low PRA and high ARR were associated with the development of CKD in a general population [15]. Diabetic nephropathy is caused by intracellular biochemical abnormalities, including hyperglycemia-induced oxidative stress, accumulation of advanced glycation end-products (AGEs), and enhancement of the polyol pathway [2,5,16]. Glomerular hypertension also plays an important role in the progression of nephropathy [16]. Impaired glomerular filtration function leads to a compensatory increase in glomerular pressure and systemic blood pressure to maintain filtration capacity [2,5]. The resulting glomerular hypertension, in turn, overloads endothelial cells and mesangial cells, with subsequent progression of glomerular damage [5]. Angiotensin II (Ang II) production increases in damaged renal

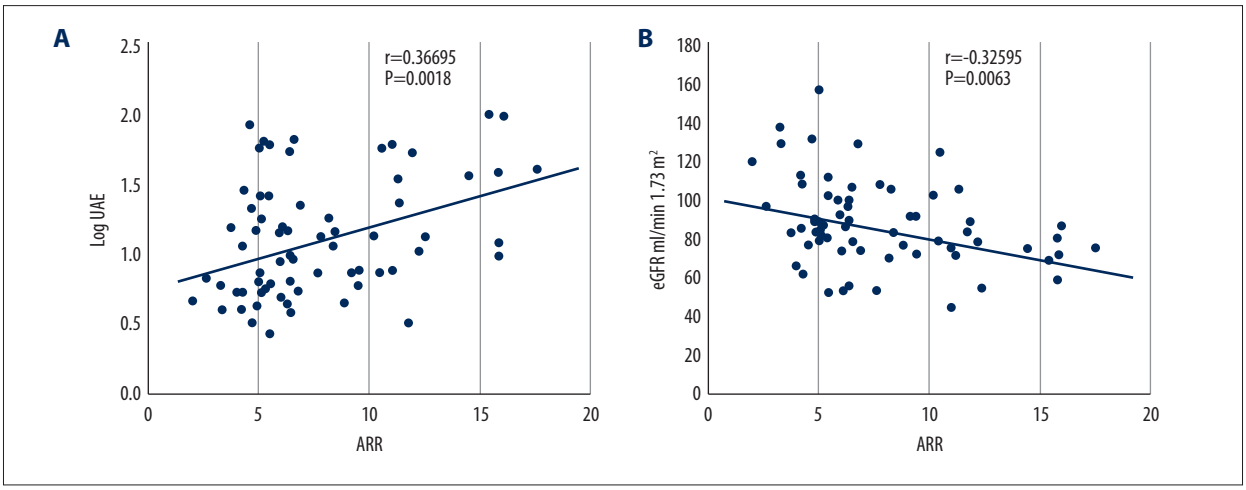

Figure 2. Correlation of aldosterone-to-renin ratio (ARR) with log UAE (A) and eGFR (B) (Paint Shop Pro, Corel Corporation). UAE – urinary albumin excretion; eGFR – estimated glomerular filtration rate.

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tissue, leading to the further development of glomerular hypertension due to increased blood pressure caused by vasoconstriction and contraction of efferent arterioles [17]. Ang II induces cytotoxic effects, such as increased TGF-β expression, and also increases aldosterone secretion [5,18]. Therefore, inhibition of the RAAS is essential to prevent the progression of nephropathy, and substantial evidence supporting this has been published [16,19,20].

On the other hand, patients with diabetes are known to present with hyporeninemia and hypoaldosteronemia [21] with the progression of renal damage, which leads to even lower PRA levels [13,15]. In the present study, PRA decreased significantly with increasing UAE levels, a finding consistent with previous reports. Aldosterone is the final hormone in the RAAS, and its balance with renin is important. Moreover, an ARR of 20 or higher is considered a screening criterion for PA [7,8]. In this study, patients with stage 1 nephropathy were divided into 2 groups: NL group with normal albuminuria, UAE of less than 10 mg/day, and the N group with upper limit normal albuminuria, UAE of 10-29 mg/day. In addition, the M group with stage 2 nephropathy was included to compare the ARR values among these 3 groups. The results showed that the ARR was significantly higher with increasing UAE in the N and M groups compared to the NL group. Furthermore, the UAE and ARR were positively correlated, suggesting that a relatively higher PAC compared to PRA may be associated with diabetic nephropathy. On the other hand, ARR is known to be higher in older adults due to PRA suppression [7]; however, no significant association between ARR and age was observed in this study. Although patients with extremely low PAC were excluded from the study, we cannot completely rule out the possibility that the ARR was high due to a decrease in PRA associated with the progression of nephropathy.

In this study, ARR showed a significant negative correlation with eGFR, suggesting that a high PAC relative to PRA may be associated with the progression of renal dysfunction. Moreover, it has been shown that aldosterone directly induces renal damage via MR in renal blood vessels, tubules, mesangial cells, renal fibroblasts, and glomerular epithelial cells independent of hypertension [22,23].

Conclusions

In patients with diabetes, high aldosterone levels relative to renin may be a risk factor for the progression of diabetic nephropathy, even if the PAC is within the normal range. However, it is unclear whether the relatively high aldosterone levels are due to increased secretion of aldosterone or increased renal production of aldosterone, and more detailed studies are needed. The present study had some limitations, as follows: 1) the number of patients was small and it was a single-center study; 2) the sample consisted of patients who required hospitalization because of poor diabetic control; 3) the patients studied were in early diabetic nephropathy. Further studies in large samples are necessary.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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