Original Articles

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Change in Proteinuria and Renal Function in Patients with Type 2 Diabetes Receiving Standard Treatment

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In patients with type 2 diabetes, proteinuria is generally considered to be a major factor in the progression to end-stage kidney disease (ESKD) and cardiovascular events. The exacerbation of proteinuria is mainly associated with high blood glucose, hypertension and dyslipidemia. This study is a single-center retrospective cohort study using a large number of patients with type 2 diabetes to investigate the correlation among proteinuria, blood glucose, blood pressure and renal function based on the standard treatment. Patients with type 2 diabetes (n=739) were divided into three groups according to their HbA1c levels, such as HbA1c < 7% ; Group L, 7%≤ HbA1c < 8% ; Group M, and 8% ≤ HbA1c; Group H. A multiple logistic regression model was used to identify the risk associated with those parameters in type 2 diabetes. There was a significant relationship between the increase of proteinuria and the unsatisfactory control of blood pressure (systolic blood pressure of more than 130 mmHg) in all patients with type 2 diabetes. Under the satisfactory control of blood glucose (HbA1c < 7% ; Group L), the annual change of proteinuria (ΔuACR/year) and renal function (ΔeGFR/year), in the patients with an sBP of less than 130mmHg with or without renin-angiotensin system inhibitor (RASI) were milder than in those patients with an sBP of more than 130 mmHg. Therefore, simultaneous strict control of HbA1c and blood pressure with or without renin-angiotensin system inhibitor (RASI) administration are essential in for maintaining renal function in patients with type 2 diabetes.

Key words: diabetic nephropathy, renin-angiotensin system inhibitor (RASI), urinary albumin creatinine ratio (uACR), estimated glomerular filtration rate (eGFR).

Introduction

Preventing the increase in proteinuria is a primary treatment objective in patients with diabetic nephropathy[1, 17, 20]. Persistent proteinuria may make this disease progress to end-stage kidney disease (ESKD).[2–3] The exacerbation of proteinuria is associated with high blood glucose (HbA1c), hypertension, obesity, a high-protein diet and other issues.[11–14, 18, 24] The effects of renin angiotensin system inhibitors (RASI) {angiotensin II type 1 receptor blockers; ARBs and angiotensin-converting enzyme inhibitors ; ACEIs} on the progression of proteinuria and control of blood pressure have been widely demonstrated in patients with type 2 diabetic nephropathy.[4] Most of international guidelines recommend ARBs or ACEIs were first choice for the treatment of hypertensive patients with type 2 diabetes.[5] Japanese guidelines also recommend treatment with ARBs or ACEIs to ameliorate proteinuria in normotensive patients with type 2 diabetes.[6]

In this study, we performed a single-center retrospective cohort study using a large number of

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patients with type 2 diabetes to investigate the correlation among proteinuria, blood pressure and renal function (eGFR) under strict control of blood glucose levels (HbA1c of less than 7.0%).[19] It is important to maintain HbA1c at less than 7% and blood pressure at less than 130/80 mmHg to inhibit decrease in renal function and occurrence of cardiovascular or cerebrovascular disease (CVD) in patients with type 2 diabetes.

Materials and Methods

Patients

A study was conducted on a cohort of patients with type 2 diabetes who had been treated in Koshigaya Municipal Hospital, Saitama, Japan from January 2012 to August 2017. Sufficient available data from blood and urine samples from 1,053 patients were analyzed in this study. All medical records were reviewed retrospectively. In this study, participants were eligible if their estimated glomerular filtration rate (eGFR), i.e. an index of renal function, was more than 30 ml/min/1.73 m^2. (eGFR is 194 x $Cr^{-1.097}$ x $Age^{-0.287}$; female x 0.739). After excluding the patients who did not meet this criterion, a remaining 739 patients (mean age: 66.9±12.3 years, mean duration of diabetes: 8.74±6.0 years) were finally evaluated in this study. These patients were divided into three groups according to their HbA1c levels: 1) a lower group (Group L) (n=325; HbA1c less than 7% , mean age : 69.2±10.5 years of age, mean duration of diabetes: 8.55±6.05 years), 2) a middle group (Group M) (n=285; 7%≤HbA1c<8%, mean age : 66.9±12.4 years of age, mean duration of diabetes: 9.0±6.07 years) and 3) a higher group (Group H) (n=129; HbA1c more than 8%, mean age: 61.4±14.8 years of age, mean duration of diabetes: 8.63±5.76 years). All patients had been receiving standard hypoglycemic agents, such as DPP-4 inhibitor, SGLT2 inhibitor, sulphonylurea, α-glucosidase inhibitor and insulin in our hospital. The urinary albumin creatinine ratio (uACR) was used for an index of proteinuria. The exacerbation of decline in renal function was defined as a decrease in eGFR levels.

Patient follow-up

A comparative analysis on the change in proteinuria and renal function was conducted using several parameters including: 1) gender, 2) treatment with or without RAS inhibitors (RASI), 3) treatment with or without statin, 4) blood pressure levels, i.e. well- controlled was defined as systemic blood pressure (sBP) of less than 130 mmHg and 5) HbA1c, for which median value during follow-up period was calculated and patients were divided into groups according to that value (HbA1c < 7% ; Group L, 7%≤ HbA1c < 8 % ; Group M, and 8% ≤ HbA1c; Group H) as described above. LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG) were also recorded.

The starting point of uACR measurement was defined as the starting time of this study, and the end point was the final measurement of uACR. uACR was periodically measured at intervals of about 6 months. The uACR levels that deviated from mean±2SD were excluded from this study. Amount of change in uACR and eGFR from the starting point to the end point was divided by each follow-up period and the obtained value was defined as annual change. The number of patients with hospitalizations due to cardiovascular or cerebrovascular events were also analyzed.

Since this study was not a clinical trial and the data were retrospective in nature and analyzed anonymously, written informed consent for participation was not obtained from the patients. This study was written after the approval was obtained from the ethical committee of our hospital. The ethical committee approval number was 2020-18.

Statistical analyses

Comparisons between groups were performed using the Mann-Whitney U-test. Comparisons between three groups of blood glucose (HbA1c) levels, i.e. Group L, M and H, were performed using the Kruskal-Wallis-U-test. A multiple logistic regression model was used to identify the risk of diabetic nephropathy associated with gender, with or without RASI, with or without Ca channel blocker and β blocker , with or without statin, systolic blood pressure (sBP<130mmHg or sBP ≥130mmHg), and LDL-C (LDL-C classified as 120 mg/dl or more and less than 120 mg/dl), HDL-C (HDL-C classified as 40 mg/dl or more and less than 40 mg/dl), TG (150 mg/dl or more and less than 150 mg/dl).

$P<0.05$ was considered to indicate statistical significance. HAPPY ACTIS version 3.13.3 and

Waha Transformer version 4.2.6.1 were used for the collection of patient data, data extraction and calculation. All statistical analyses were performed using the Easy R version 1.36. EZR is freely available on the homepage of Jichi Medical University Saitama Medical Center. Statistical functions have been added to the R commander.

Results

Analyses of several biomarkers based on HbA1c levels

1) Comparing Group L with other groups

Mean eGFR levels in Group L were lower than those in the other two groups. Mean HDL-C levels and the number of patients with RASI in Group L were relatively higher than those in the other two groups.

2) Comparing Group M with other groups

Mean LDL-C and TG levels in Group M during the measurement period were significantly higher than those in the other two groups.

3) Comparing Group H with other groups

Mean age were significantly younger than those in the other two groups. Mean sBP were statistically significantly higher than those in the other two groups ($p<0.001$). Mean uACR levels were higher than those in the other two groups. There was no statistically significant difference in the number of patients administered statin, gender, duration of diabetes and measurement period among Groups L, M and H (Table 1).

The annual change in proteinuria and renal function in all patients, and in Groups L, M and H

1) Comparing the annual change in uACR and eGFR in all patients

The annual change in proteinuria (ΔuACR/year) in the patients who had an sBP of less than 130 mmHg (12.1 mg/g･Cr/year) was significantly lower than those who had an sBP of more than 130 mmHg (27.8 mg/g･Cr/year) ($p<0.001$) (Figure 1). The annual change in eGFR (ΔeGFR/year) in the patients with RASI (−0.7mL/min/1.73m^2) was not significantly less than that in the patients without RASI (−2.3 mL/min/1.73m2) ($p<0.001$) (Figure 2).

2) Comparing the annual change in uACR and eGFR in Groups L, M and H

ΔuACR/year in Group L patients who had an

Table 1 Clinical characteristics of the diabetic subjects

HbA1c level		Population (n=739)	Group L (n=325)	Group M (n=285)	Group H (n=129)	P-value
Gender	male/female	334/405	202/123	126/159	59/70	0.167
Age	years (mean)	66.9±12.3	69.2±10.5	66.9±12.4	61.4±14.8	<0.001
Duration of diabetes	years (mean)	8.74±6.0	8.55±6.05	9.00±6.07	8.63±5.76	0.182
HbA1c level	% (mean)	7.24±1.03	6.41±0.39	7.42±0.27	8.93±0.91	<0.001
Follow up period	years (mean)	2.24±0.99	2.30±1.08	2.26±0.95	2.05±0.78	0.134
Systolic blood pressure	mmHg (mean)	132.3±12.0	130.6±10.4	132.8±11.4	135.5±13.4	<0.001
sBP≧130	(%)	36.0% (267/739)	29.7% (94/325)	39.0% (108/285)	49.6% (64/129)	<0.001
RASI administration	(%)	51.8% (267/739)	57.8% (188/325)	48.4% (138/285)	44.2% (57/129)	0.0109
Statin administration	(%)	44.1% (326/739)	46.8% (152/325)	41.8% (119/285)	42.7% (55/129)	0.431
LDL cholesterol	mg/dl (mean)	109.6±26.6	108.8±24.9	112.9±28.1	104.4±26.8	0.022
HDL cholesterol	mg/dl (mean)	56.4±15.6	58.0±15.8	55.0±14.8	55.3±15.0	0.004
Triglycerides	mg/dl (mean)	109.6±26.6	108.8±24.9	113.0±28.1	104.4±26.8	0.021
uACR	mg/g･Cr (mean)	75.8±162.2	51.6±310.7	75.1±194.2	138.2±182.7	<0.001
eGFR	ml/min/1.73㎡ (mean)	70.9±18.8	66.8±37.2	72.9±19.7	76.7±19.7	<0.001

Age, Duration of diabetes, HbA1c, follow up period, systolic blood pressure, LDL-cholesterol values, HDL-cholesterol values, Triglycerides values, uACR and eGFR indicated by the mean ±SD. All subjects (n=739) classified into three groups according to the HbA1c level. sBP≧130, RASI administration, Statin administration, indicated by percentages. eGFR: estimated glomerular filtration rate. uACR: urine Albumin Creatinine Ratio. P<0.05 was consideration to be statistically significant (Kruskal-Wallis-test).

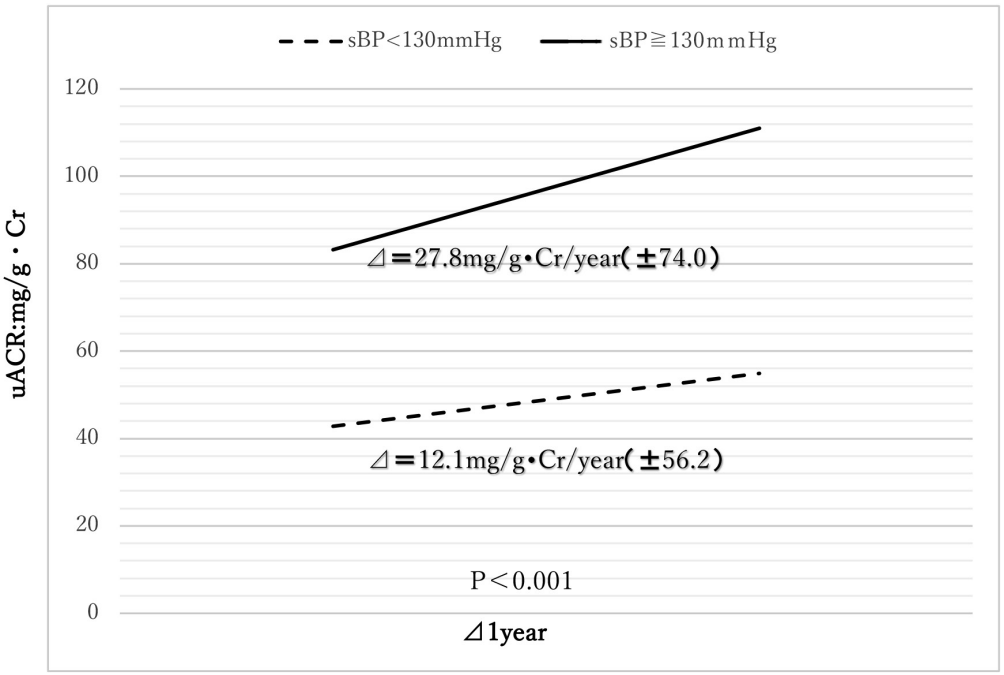


Figure 1 estimated change in uACR of study population
Comparison between groups in the estimated amount of change in uACR (mg/g・Cr) due to systolic blood pressure difference. uACR: mean ±SD. P<0.05 was consideration to be statistically significant (Mann-Whitney U-test).
uACR had significantly increased in patients with sBP of more than 130 mmHg.

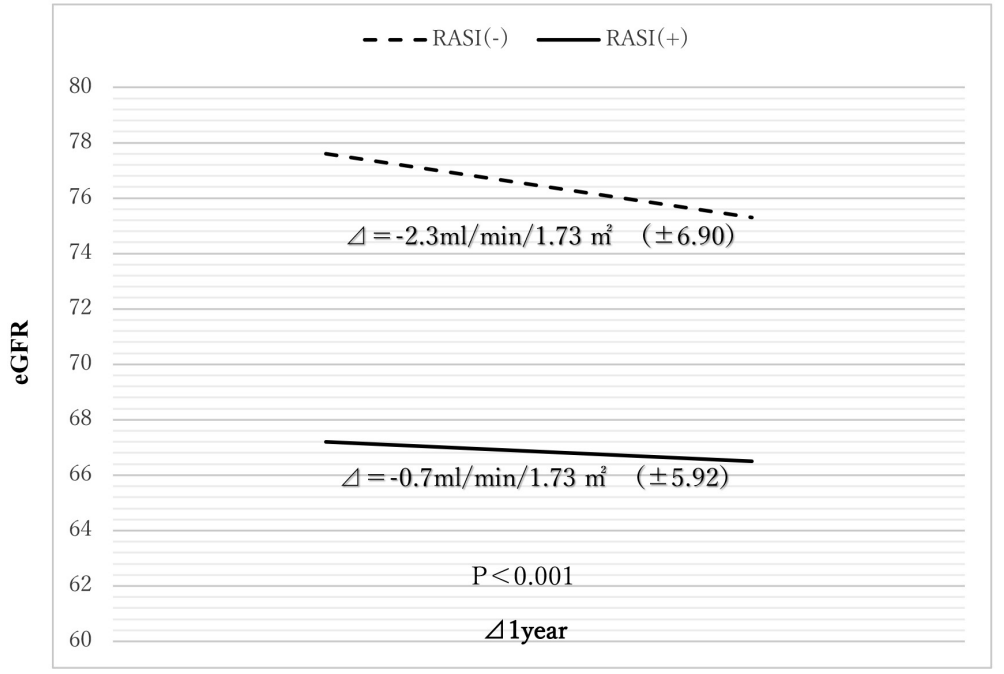


Figure 2 estimated change in eGFR of study population
Comparison between groups in the estimated amount of change in eGFR (ml/min/1.73㎡) based on RASI administration. eGFR: mean ±SD. P<0.05 was consideration to be statistically significant (Mann-Whitney U-test).
eGFR had significantly decreased in patients without RASI.

sBP of less than 130 mmHg (13.1 mg/g･Cr/year) was significantly lower than those who had an sBP of more than 130 mmHg (230.9 mg/g･Cr/year) (p<0.001) (Figure 3). There was no significant change in ΔuACR between both sBP levels in Groups M and H. ΔeGFR/year in Group L patients with RASI (0.9mL/min/1.73m^2) was significantly higher than in those without RASI (−2.0 mL/min/1.73m^2) (p<0.001) (Figure 4). There was no significant change in ΔeGFR/year between patients treated with or without RASI in Groups M and H. In Group L, the levels of ΔuACR/year in the patients with an sBP of less than 130mmHg with or without RASI were lower than in those patients

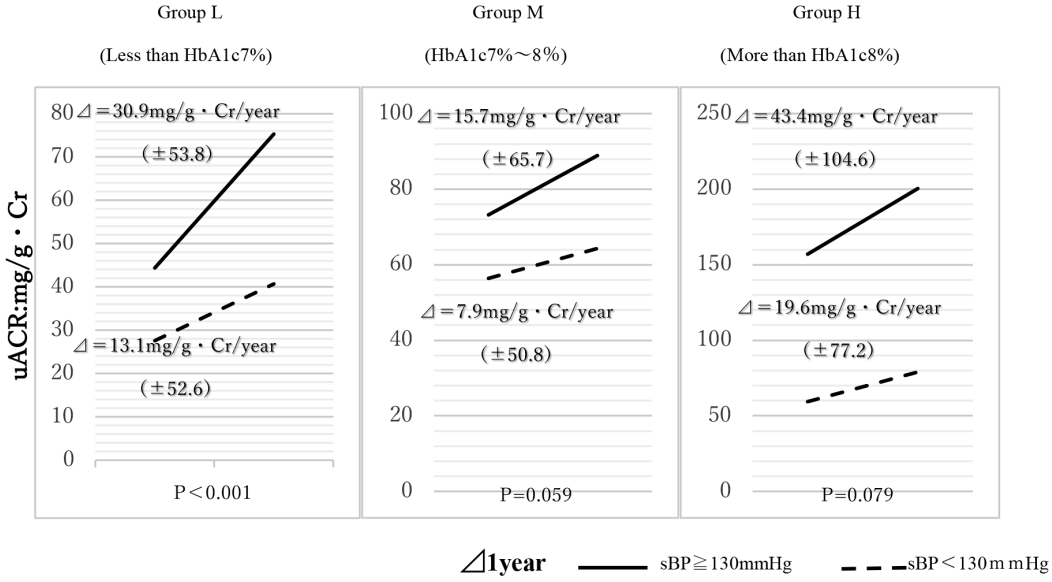


Figure 3 estimated change in uACR of each group. (L, M and H groups)
Comparison between groups in the estimated amount of change in uACR (mg/g・Cr) due to systolic blood pressure differences. uACR: mean ±SD. P<0.05 was consideration to be statistically significant (Mann-Whitney U-test). uACR had increased in patients with sBP of more than 130 mmHg in any of these groups, while significant difference was noted only in Group L.

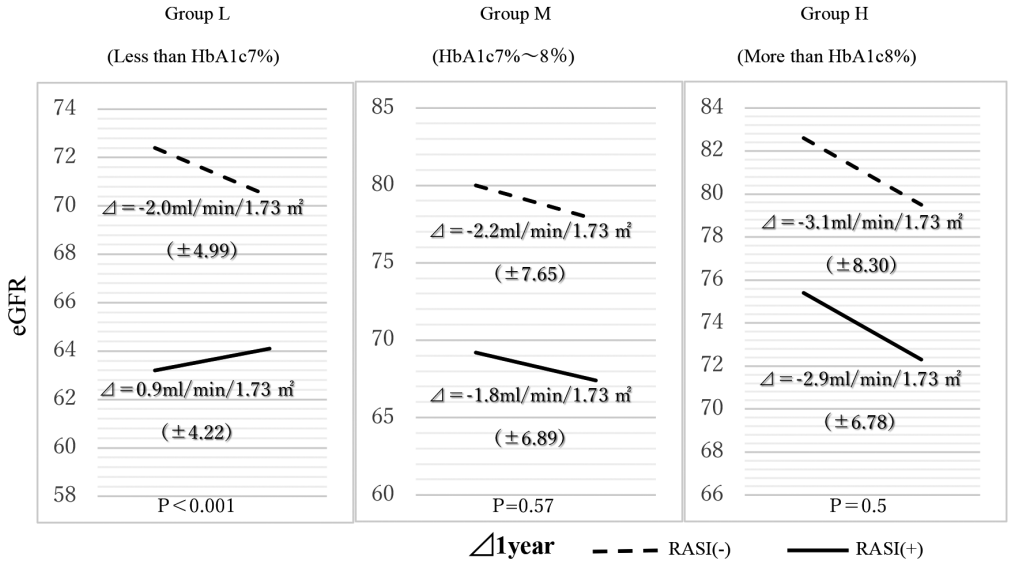


Figure 4 estimated change in eGFR of each group. (L, M and H groups)
Comparison between groups in the estimated amount of change in eGFR (ml/min/1.73㎡) based on RASI administration. eGFR: mean ±SD. P<0.05 was consideration to be statistically significant (Mann-Whitney U-test).
In patients with RASI, eGFR did not decrease only in patients included in Group L.

with an sBP of more than 130 mmHg without RASI. In Group L, the levels of ΔeGFR/year in the patients with an sBP of more or less than 130mmHg with RASI were higher than those in the patients with sBP of more or less than 130 mmHg without RASI (Table 2).

Comparison of odds ratio by a logistic regression analysis in Group L

1) uACR

Odds ratio of increase in uACR in patients with sBP of more than 130 mmHg compared to patients with sBP of less than 130 mmHg was 7.38 (95% CI: 4.17–13.10) ($p<0.05$), showing significant difference (Table 3). No significant difference was observed in comparison of other contributing factors (with or without oral drugs such as RASI or statin; LDL-C levels, HDL-C levels, and TG levels).

2) eGFR

Odds ratio of decrease in eGFR in patients with RASI compared to patients without RASI was 0.264 (95% CI: 0.15–0.46) ($p<0.05$) (Table 4), showing significant difference. No significant difference was observed in comparison of other contributing factors (difference in sBP, with or without oral drug such as statin, LDL-C levels, HDL-C levels, and TG levels).

Number of patients who were hospitalized due to a cardiovascular or cerebrovascular event in Group L

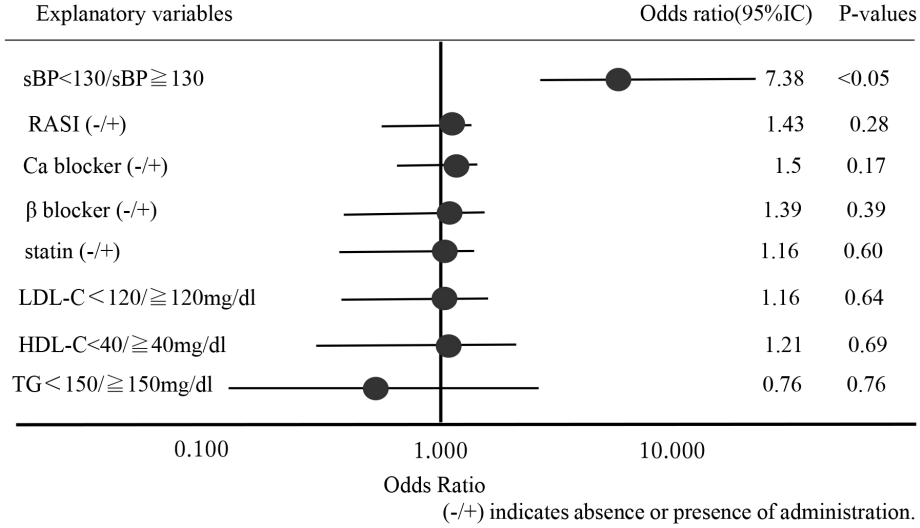
The number of patients with an increase in uACR who were hospitalized due to a cardiovascular or cerebrovascular event was 4.2 per 1,000

Table 2 Four groups were created based on systolic blood pressure and presence of RASI administration in Group L

	sBP<130+RASI(−) (n=107)	sBP≧130+RASI(−) (n=23)	sBP<130+RASI(+) (n=115)	sBP≧130+RASI(+) (n=71)	P-value
Gender (male/female)	65/42	11/12	74/41	46/25	
Age (average years)	66.6±11.7	68.3±11.9	68.3±11.6	71.8±10.4	
Duration of diabetes (year)	8.70±5.99	9.87±11.9	9.46±6.01	9.87±5.73	
uACR annual estimated change (ml/min/1.73㎡)	10.2±58.1	29.8±50.8	15.9±47.1	31.3±55.1	
eGFR annual estimated change (ml/min/1.73㎡)	−2.09±4.84	−0.96±5.71	0.9±4.31	0.95±4.12	<0.001*

n=325 (no data =9) Age, Duration of diabetes, Annual estimated amount of change in uACR, Annual estimated amount of change in eGFR indicated by the mean ±SD. Annual estimated change (⊿1 years). P<0.05 was consideration to be statistically significant (Kruskal-Wallis-test). *:In patients with sBP of more than 130mmHg, amount of change in eGFR had significantly decreased in patients without RASI compared to that in patients with RASI. ($p<0.001$).

Table 3 A factor analysis using logistic regression was performed on the increase in uACR for group L



(-/+) indicates absence or presence of administration.

Table 4 A factor analysis using logistic regression was performed on the decrease in eGFR for group L

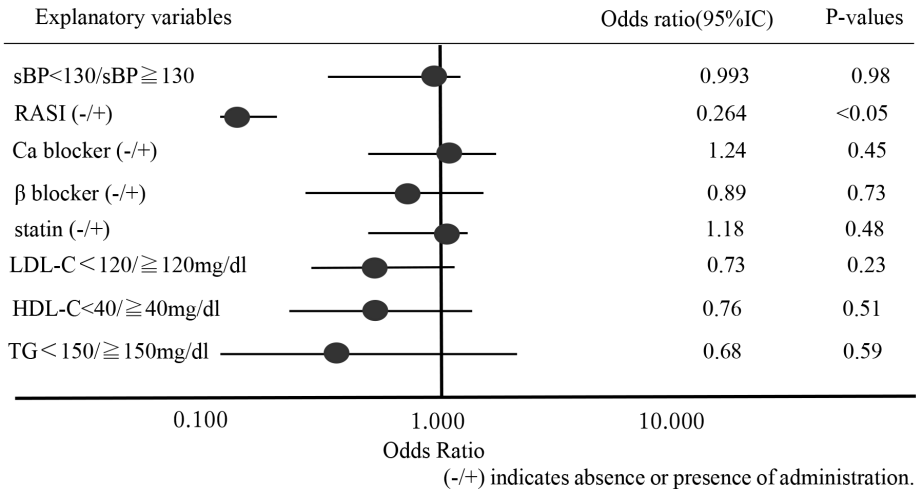
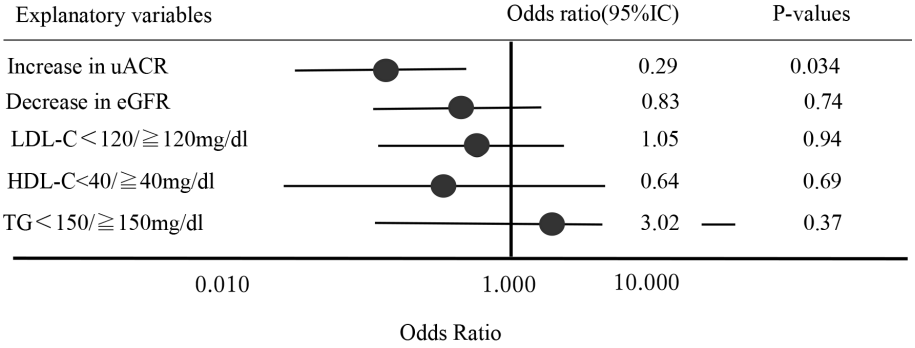


Table 5 A factor analysis was performed on the number of patients who were hospitalized due to cardiovascular or cerebrovascular events



person-years using the person-years method. For patients without increased uACR, this was 2.8 per 1,000 person-years.

The odds ratio of patients without an increase in uACR was 0.29 (95%CI 0.07-0.96) (Table 5). The patients in Group L with a decrease in uACR did not require hospitalization. No significant difference was observed in comparison of other contributing factors (difference in sBP, with or without of oral drugs such as statin, LDL-C levels, HDL-C levels, and TG levels).

Discussion

This study includes 739 patients who are receiving outpatient treatment at a single hospital and relatively advanced in age (mean age of residents: 66.9±12.3 years) as a target population. And this study is characterized by a capability of following up treatment progress in these patients over time. We examined the correlation among blood glucose (HbA1c), systolic blood pressure, urinary protein (uACR) and renal function (eGFR) to identify the risk factors for development of nephropaty in patients with type 2 diabetes.

In addition to type 2 diabetes, decreased renal function and increased proteinuria are known to induce cardiovascular and cerebrovascular events, and the result of this study were consistent with that finding.[21-23] A positive correlation was observed between the increase in proteinuria and the risk for cardiovascular or cerebrovascular disease (CVD) events.[9, 10, 15, 16] Our results suggest that the decrease in urinary protein excretion under strict blood glucose control may inhibit the occurrence of CVD events, and *vice versa*.

ΔuACR/year and ΔeGFR/year in patients with an sBP of less than 130 mmHg were milder than in patients with an sBP of more than 130 mmHg. There was a strong relationship between the increase in proteinuria and the unsatisfactory control of blood pressure (sBP of more than 130 mmHg). Several biomarkers were evaluated in

patients with type 2 diabetes grouped according to their blood glucose levels, including HbA1c < 7%; Group L, 7%≤ HbA1c < 8 %; Group M, and 8% ≤ HbA1c; Group H. uACR and eGFR levels in patients with well controlled HbA1c levels (Group L) was significantly lower than in those with moderately or poorly controlled HbA1c levels (Groups M or H). The levels of urinary protein and sBP were increased in patients with poorly controlled HbA1c (Group H). As a reason for lower eGFR in Group L compared to other groups, involvement of increased filtration through remaining normal glomeruli associated with decrease in the number of normal glomeruli, that is, hyperfiltration in a process of deterioration of renal function was assumed.[25, 26]

ΔuACR/year was significantly higher in patients with sBP of more than 130 mmHg than in patients with sBP of less than 130 mmHg even in Group L with good controlled HbA1c levels. ΔeGFR/year had significantly decreased in patients without RASI than in patients with RASI even in Group L. It was suggested that lowering blood pressure prevents proteinuria from increasing and that oral administration of RASI maintains renal function.

In this study, however, blood pressure control maintaining sBP at 130 mmHg is required to decrease proteinuria. Therefore, it was considered that there are some issues that should be resolved. Especially, the condition in majority of the elderly is considered to be complicated by arteriosclerosis lesion, and thus a possibility that treatment easily leads to excessive lowering of blood pressure should be considered to perform blood pressure control in this population group. How the target hypotensive level (130 mmHg) should be achieved became a future issue.

The treatment targets in patients with type 2 diabetes are set as HbA1c of lower than 7% and blood pressure of less than 130/80 mmHg in our hospital[8], but in this study, these targets were achieved in approximately 30% of the patients (n=222/739) and kidney protecting effect of drug was commonly insufficient even in patients who receives treatment with RASI. In order to obtain sufficient drug effect, strict treatment target should be achieved. Furthermore, it is considered necessary to take measures to prevent adverse events associated with the treatment drugs such as excessive lowering of blood pressure or severe hypoglycemia.

This study had some limitations and difficulties: 1) it was a retrospective single-center study, 2) there may have been unintended selection bias or potential bias and 3) small numbers of patients after classification by each factor. Therefore, the results of this study need to be confirmed by the prospective study.

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Authors' contributions

GK conceived the study, participated in the study design and analyzed the data. SS and SY analyzed the data. YM, TY and YS conceived and participated in the study design and critically reviewed the manuscript.

Conflicting interest statement

The Authors declare that there is no conflict of interest.

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