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ORIGINAL ARTICLE

Temporal trends in the prevalence of albuminuria and reduced eGFR in Japanese patients with type 2 diabetes

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Abstract

Changes over time have been shown in renal manifestations in individuals with diabetes in the United States; however, whether the trends are shared across ethnicities is unknown. We conducted this single-center serial cross-sectional study to determine temporal changes in albuminuria and reduced kidney function in Japanese patients with type 2 diabetes. This study included adult Japanese patients with type 2 diabetes who first visited our institute between 2004 and 2013. Temporal changes during the 10 years in the frequency of albuminuria (≥ 30 mg/g creatinine) and reduced eGFR (< 60 mL/min/1.73 m^2) were analyzed using the univariate and multivariate logistic regression analyses and Granger causality test. 5331 Japanese patients with type 2 diabetes, 1892 women and 3439 men, with the mean age of 56 ± 13 years, were studied. There was no change in the prevalence of albuminuria in the univariate analysis; however, a significantly decreasing trend was observed after adjustment for several covariates. On the other hand, patients with reduced eGFR significantly increased over time, although the statistical significance disappeared after adjustment for the covariates, including levels of serum uric acid and hemoglobin and use of renin–angiotensin inhibitors. The Granger causality test showed that time series for use of RAS inhibitors and BMI had a causative role in time series for reduced eGFR. In conclusion, prevalence of albuminuria decreased and that of reduced eGFR remained stable after adjustment for clinical characteristics in Japanese patients with type 2 diabetes during the last decade.

Keywords Albuminuria · eGFR · Type 2 diabetes · Granger causality

Introduction

Nephropathy is one of the most serious complications of both type 1 and type 2 diabetes. Previous studies have shown that the natural course of nephropathy differs between type 1 and type 2 diabetes mellitus [1–10]. In type 1 diabetes, urinary albumin excretion first increases and subsequently glomerular filtration rate (GFR) starts to decrease [5]. In type 2 diabetes, on the other hand, a considerable number of patients already exhibit reduced GFR at the diagnosis of type 2 diabetes [6]. Longitudinal and cross-sectional studies [6–10], including ours, [4, 9] have found that reduction of GFR precedes the onset of albuminuria in patients with type 2 diabetes.

Recently, the National Health and Nutrition Examination Survey in the United States (NHANES) has shown an increasing trend in the prevalence of reduced GFR and a decreasing trend in the prevalence of albuminuria among overall adult patients with type 2 diabetes in the United States during the last 26 years [11, 12]. However, significant heterogeneities were observed among ethnicities, remaining unclear whether the temporal changes in the phenotype of renal parameters are shared beyond ethnicities [12, 13]. In addition, there was no change in the prevalence of albuminuria among elderly people [12].We, therefore, conducted this single-center serial cross-sectional study to explore whether the renal phenotype of Japanese patients with type 2 diabetes has similarly changed. We also aimed to determine clinical characteristics and patient background associated with the temporal changes.

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Patients and methods

Subjects

This was a single-center serial cross-sectional study, including Japanese patients who (1) had type 2 diabetes (2) were ≥ 20 years of age (3) first visited the Diabetes Center, Tokyo Women's Medical University, Tokyo Japan, during the period between 2004 and 2013 (4) had serum creatinine and urinary albumin levels measured within 3 months after the initial presentation (5) exhibited an estimated GFR (eGFR) ≥ 15 mL/min/1.73 m^2, and (6) underwent an assessment of the presence and stage of diabetic retinopathy by ophthalmologists. The period from the diagnosis of diabetes and the first visit to the hospital was not restricted. Patients who were treated with dialysis, had undergone kidney transplantation, or were pregnant were excluded.

The present study was conducted as a part of the Prospective Cohort Study Elucidating Factors Associated with the Pathogenesis, Prognosis, and Prognosis of Diabetic Nephropathy conducted in Diabetes Center, Tokyo Women's Medical University, the protocol of which was approved on April 25, 2009 by the Ethics Committee of Tokyo Women's Medical University School of Medicine (Approval No. 1584). Since this was an observational but not a prospective intervention study, the Ethics Committee provided a waiver of informed consent.

Measurements

Urinary albumin was measured in the first morning urine with the immunoturbidimetry method, serum and urinary creatinine levels were measured using the enzymatic method, LDL and HDL cholesterol were measured by the homogenous assays, triglycerides were measured by the enzymatic colorimetric method, uric acid was measured by the uricase method; these measurements were performed using an autoanalyzer (Hitachi Labospect 008, Hitachi, Tokyo). Glycated hemoglobin (HbA1c) was measured by the HPLC using a fully automated HbA1c analyzer (ADAMS A1c HA-8180, Arkray, Inc., Kyoto). Urinary albumin was divided by urinary creatinine to calculate the urinary albumin-to-creatinine ratio (UACR).GFR was estimated (eGFR) using the formula proposed by the Japanese Society for Nephrology [14]. Clinical findings and laboratory data were collected from the hospital medical records.

The geometric mean levels of urinary albumin, arithmetic mean of eGFR, and frequencies of patients with albuminuria, defined as UACR ≥ 30 mg/g, and reduced kidney function, defined as eGFR < 60 mL/min/1.73 m^2 were calculated for each year.

Statistical analysis

Data were expressed as mean ± standard deviation (SD), geometric mean, or frequency. Changes over time in the frequency of albuminuria, reduced kidney function, and other binary data were examined using (1) the single regression analysis with the first-visiting calendar year treated as an independent continuous variable, (2) the Cochran–Armitage trend test, and (3) univariate logistic regression analysis. Changes over time in continuous variables were examined using the Jonckheere–Terpstra trend test.

Trends in the frequency of the renal parameters were also examined using the multivariate logistic regression analysis, after adjustment for age, sex, diabetes duration, smoking history, presence of retinopathy, history of coronary artery disease and stroke, use of renin–angiotensin system (RAS) inhibitors, body mass index (BMI), systolic blood pressure, diastolic blood pressure, hemoglobin, HbA1c, serum levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, logarithmically transformed triglycerides, and uric acid, without variable-selection procedures. Continuous variables were standardized by converting the data to yield mean of 0 and SD of 1. Strengths of contribution among the variables in the multivariate logistic regression analysis were compared by the Wald Chi-square test.

As a sensitivity analysis, logistic regression analysis after adjustment for propensity score was also performed. The propensity score in each patient was calculated using the above 17 covariates and incorporated in the logistic model as a solitary covariate.

Causality between time-series data was examined using the Granger causality test, which was originally developed to analyze econometric data as a method for detecting causal correlations between time-series data [15]. This test has been recently used widely in medical research of the field of neurology, particularly neural networks [16]. In the present study, the null hypothesis verified by the Granger causality test was that the time-series data for the frequency of albuminuria or reduced eGFR (X) was influenced by X itself, and not by other time-series data (Y) such as changes in age. Rejection of this null hypothesis suggests that changes in X over time are affected by the time-series data on Y and that including Y time-series data may enable more accurate predictions of how the frequency X will change over time.

SAS/STAT 14.3 (SAS Institute, Inc., Cary, NC) was used for the statistical analyses.

Results

We studied a total of 5331 Japanese patients with type 2 diabetes, 1892 women and 3439 men, with the mean age of 56 ± 13 years, ranging 20–90 years, who met the above criteria. As shown in Table 1, no significant trend was observed in age or sex over the 10-year period. The number of patients taking anti-hypertensive drugs and RAS inhibitors significantly increased over time, with the rate of annual increase of 1.3% and 1.8%, respectively. No significant trends were observed in the frequency of patients with a history of coronary artery disease or stroke. There was a significantly increasing trend in patients having retinopathy, with the increase rate of 1.0% per year. Significantly increasing trends were also observed for the mean levels of BMI, uric acid, LDL cholesterol, and HDL cholesterol. A significantly decreasing trend was observed for diastolic blood pressure.

The geometric mean levels of urinary ACR exhibited a significantly decreasing trend over the 10-year period when examined using the Jonckheere–Terpstra test (Table 1; $p < 0.001$). When albuminuria was treated categorically (binary data), no significantly increasing trend was observed in the frequency of patients with albuminuria in the single regression analysis (Fig. 1a: $p = 0.956$) or the Cochran–Armitage trend test ($p = 0.981$). In the univariate logistic regression analysis, the first-visiting calendar year was not associated with increased prevalence of albuminuria; however, after adjustment for other clinical data in the multivariate analysis, the first visit year became statistically significant with an odds ratio (OR) of 0.966 per year (Table 2, $p = 0.029$). The logistic regression analysis after adjustment for the propensity score that was calculated using the 17 covariates yielded the identical association between calendar year and prevalence of albuminuria (Table 2).

Mean levels of eGFR decreased significantly over the 10-year period (Table 1; Jonckheere–Terpstra test for trend: $p = 0.001$), with the number of patients with eGFR < 60 mL/min/1.73 m^2 increasing significantly ($p = 0.005$; Cochran–Armitage test for trend: $p < 0.001$; univariate logistic regression analysis: OR, 1.05; $p < 0.001$). However, the statistical significance for the first-visit year disappeared after adjustment for the covariates as well as for the propensity scores (Table 2).

Other variables significantly associated with the presence of albuminuria and with reduced eGFR are listed in Table 2. According to the Wald Chi-square, the following factors had higher predictability for albuminuria in descending order: presence of retinopathy, hemoglobin level, systolic blood pressure, and HbA1c. The factors with higher predictability for reduced eGFR were as follows in descending order: serum uric acid level, age, hemoglobin, and use of RAS inhibitors.

Finally, the Granger causality test was used to examine the time-series data that affected the time-series data on the frequency of patients with albuminuria and reduced kidney function. As shown in Table 3, only the time series for age significantly impacted the changes in albuminuria over time. The time series for use of RAS inhibitors and BMI was factors that influenced the time-series data on reduced eGFR. Of these, BMI and reduced eGFR had a bidirectional relationship. All other factors were one-way causalities.

Discussion

This single-center serial cross-sectional study aimed to determine whether the frequency of albuminuria and reduced kidney function changed significantly during the last 10 years in Japanese patients with type 2 diabetes. The univariate analysis showed that the frequency of patients with albuminuria did not change; however, the multivariate analysis yielded a significant decreasing trend. In contrast, while the apparent frequency of patients exhibiting reduced kidney function (eGFR < 60 mL/min/1.73 m^2) increased significantly, the significance disappeared in the multivariate analysis. In the Granger causality test, which was used to infer causality between time series, there was a significant causality between the time series on albuminuria and age and between the time series on reduced kidney function and the use of RAS inhibitors and BMI.

Our findings appear to be consistent with epidemiological studies from the NHANES [11, 12], as well as a single-center study reported most recently from Japan [13]. However, in the study from the NHANES, the prevalence of reduced eGFR was only adjusted for age, sex, and ethnicity but not for the use of RAS inhibitors [12]. The Japanese group has simply examined covariation showing only crude incidence of renal parameters over time, lacking considerations of the correlation or association between the trends [13]. Although both of these authors speculated that decreased incidence of albuminuria and increased incidence of reduced kidney function were associated with increased incidence of use of the RA inhibitors [12, 13], the associations were not examined by appropriate statistical analyses. In our study, the associations were examined by multiple logistic regression analysis and Granger causality test. Pharmacological blockade of the RAS by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers acutely reduce intraglomerular pressure and GFR by dilating the afferent arterioles of the renal glomeruli [17, 18]. Relatively recent guidelines for hypertension have recommended RAS inhibitors as the first-line therapy for hypertension in patients with diabetes regardless of albuminuria [19–21], promoting physicians to prescribe RAS inhibitors more preferentially. This may help explain, at least in part,

Table 1 Temporal trends in clinical characteristics and laboratory data during 10 years

	First-visit year										*P* value
	2004 (*N* = 632)	2005 (*N* = 664)	2006 (*N* = 609)	2007 (*N* = 508)	2008 (*N* = 556)	2009 (*N* = 490)	2010 (*N* = 520)	2011 (*N* = 485)	2012 (*N* = 430)	2013 (*N* = 437)	
Age (years)	55.4	56.3	57.0	55.5	55.3	55.6	57.0	56.1	57.3	55.8	0.394
Women (%)	36.9	36.5	35.1	35.2	32.9	37.8	34.2	34.4	34.9	36.8	0.642
Diabetes duration (years)	6.0	6.4	6.7	5.5	6.8	7.2	6.9	7.7	6.7	7.0	0.051
Current smoker (%)	54.9	53.5	54.6	56.0	57.8	52.0	54.3	54.0	48.6	52.9	0.154
Hypertension (%)	59.0	64.6	62.2	74.1	66.2	63.9	64.6	61.4	63.1	65.6	0.438
Use of antihypertensive agents (%)	30.1	30.5	30.1	31.3	36.2	36.3	41.5	37.5	40.2	38.5	< 0.001
Use of RA system blockers (%)	16.2	18.6	17.5	18.5	25.7	25.8	29.9	30.2	27.4	31.7	< 0.001
History of cardiovascular diseases (%)	8.5	12.6	15.1	9.8	12.5	10.6	10.1	8.7	13.5	11.4	0.917
History of coronary heart diseases (%)	5.7	6.4	9.5	6.2	7.0	5.0	6.7	3.2	8.3	6.9	0.619
History of stroke (%)	4.1	6.6	6.1	4.0	6.8	6.5	3.8	6.1	6.0	5.5	0.795
Retinopathy (%)	28.8	31.6	31.4	30.9	39.2	37.1	41.0	40.6	33.5	38.2	< 0.001
Systolic blood pressure (mmHg)	144	142	142	142	143	142	141	143	142	142	0.328
Diastolic blood pressure (mmHg)	82	83	82	82	83	82	82	80	81	81	< 0.001
Body mass index (kg/m^2)	24.9	25.2	25.4	25.5	25.4	25.8	25.6	25.9	25.7	25.7	< 0.001
HbA1c (%)	8.6	8.7	8.6	8.4	8.6	8.5	8.4	8.4	8.6	8.7	0.487
HbA1c (mmol/mol)	70	71	70	68	70	69	68	68	70	71	0.487
Hemoglobin (g/dL)	14.4	14.3	14.3	14.3	14.3	14.2	14.1	14.4	14.4	14.4	0.807

Table 1 (continued)

	First-visit year										*P* value
	2004 (*N* = 632)	2005 (*N* = 664)	2006 (*N* = 609)	2007 (*N* = 508)	2008 (*N* = 556)	2009 (*N* = 490)	2010 (*N* = 520)	2011 (*N* = 485)	2012 (*N* = 430)	2013 (*N* = 437)	
Uric acid (mg/dL)	5.1	5.1	5.2	5.2	5.4	5.2	5.3	5.3	5.3	5.5	< 0.001
LDL cholesterol (mg/dL)	118	124	121	123	120	119	121	123	125	127	0.014
HDL cholesterol (mg/dL)	51	51	52	52	52	51	51	52	55	54	< 0.001
Triglycerides (mg/dL)	143	135	136	137	137	142	140	137	137	148	0.702
Urinary ACR (mg/g)	22.9	22.0	21.1	20.8	25.9	21.2	22.0	16.8	14.3	15.5	< 0.001
Creatinine (mg/dL)	0.77	0.76	1.78	0.77	0.81	0.79	0.84	0.79	0.79	0.85	0.002
eGFR (mL/min/1.73 m^2)	81.0	81.7	79.8	82.1	80.5	81.2	77.1	82.9	79.4	75.0	0.001

Continuous data were expressed as mean or geometric mean (for triglycerides and urinary ACR) and analyzed using Jonckheere–Terpstra trend test. Binary data were shown as percent and analyzed using Cochran–Armitage trend tests

RA renin–angiotensin, *HbA1c* hemoglobin A1c, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *ACR* albumin-to-creatinine ratio

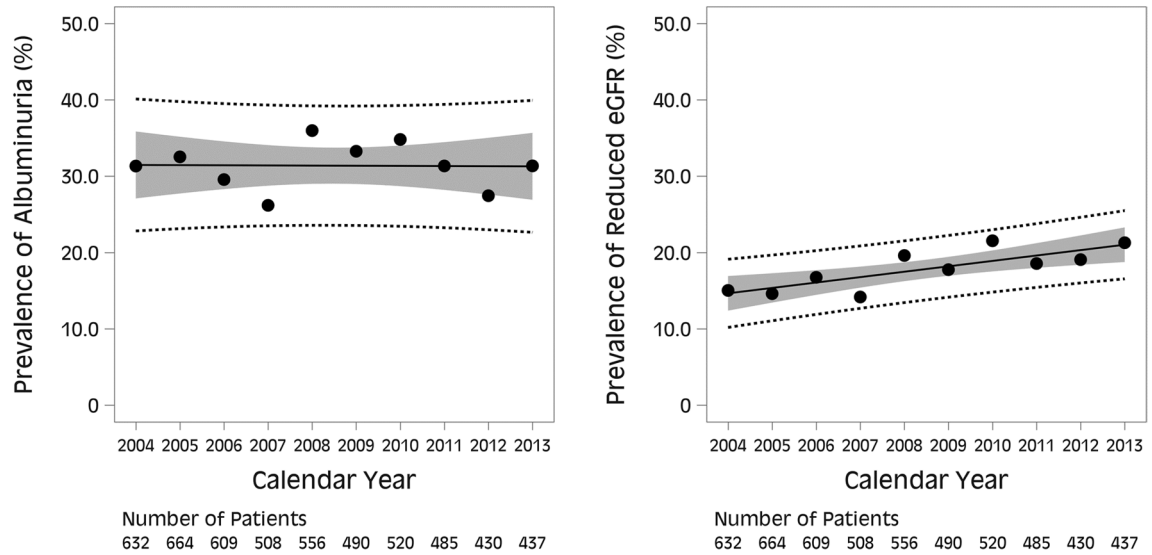

Fig. 1 Serial changes in the frequency of patients with albuminuria (≥30 mL/min/1.73 m^2, left panel) and reduced eGFR (<60 mL/min/1.73 m^2, right panel) in patients with type 2 diabetes who first visited between 2004 and 2013. Shaded area indicates 95% confidence interval of the regression line and dashed lines indicate lower and upper limit of 95% predictive interval

Table 2 Univariate and multivariate logistic regression analysis examining the associations of prevalence of albuminuria and reduced eGFR with calendar year

Variable	Albuminuria			Wald Chi-square	Reduced eGFR			Wald Chi-square
	Odds ratio	95% CI	*p* value		Odds ratio	95% CI	*p* value	
Univariate								
First-visit year	1.000	0.980–1.021	0.981	0.0	1.050	1.025–1.077	<0.001	15.5
Multivariate								
First-visit year	0.966	0.936–0.996	0.029	4.8	1.030	0.986–1.075	0.185	0.2
Age	1.053	0.937–1.184	0.385	0.8	3.281	2.727–3.948	<0.001	158.6
Male gender	1.361	1.071–1.730	0.012	6.4	1.672	1.211–2.308	0.002	9.8
Diabetes duration	1.090	0.991–1.199	0.075	3.2	1.075	0.955–1.209	0.232	1.4
Smoking	1.433	1.171–1.754	0.001	12.2	0.825	0.628–1.085	0.167	1.9
Retinopathy	3.801	3.137–4.605	<0.001	185.9	1.694	1.282–2.221	<0.001	14.6
BMI	1.143	1.031–1.267	0.012	6.5	1.351	1.141–1.516	<0.001	14.3
Use of RAS inhibitors	1.420	1.150–1.754	0.001	10.6	1.874	1.453–2.416	<0.001	23.4
SBP	1.502	1.320–1.709	<0.001	38.0	0.976	0.831–1.148	0.772	0.1
DBP	0.905	0.796–1.028	0.125	2.4	1.208	1.021–1.419	0.028	4.9
Hemoglobin	0.641	0.573–0.718	<0.001	60.0	0.436	0.376–0.507	<0.001	118.5
HbA1c	1.321	1.200–1.455	<0.001	32.0	0.920	0.798–1.061	0.253	1.3
Uric acid	1.262	1.140–1.397	<0.001	20.2	2.623	2.268–3.033	<0.001	168.8
Triglycerides	1.268	1.142–1.408	<0.001	19.9	1.386	1.197–1.605	<0.001	19.0
PS-adjusted								
First-visit year	0.966	0.938–0.996	0.028	4.9	1.029	0.987–1.073	0.159	1.78

BMI body mass index, *RAS* renin–angiotensin system, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HbA1c* hemoglobin A1c, *CI* confidence interval, *AUROC* area under the receiver operating characteristic curve, *PS* propensity score

Table 3 Granger causality test examining the association of temporal trend in clinical characteristics and laboratory data with temporal tend in albuminuria and reduced eGFR

Temporal trend in X	Temporal trend in albuminuria (Y)				Temporal trend in reduced eGFR (Y)			
	From X to Y*		From Y to X*		From X to Y*		From Y to X*	
	Chi-square	*p* value	Chi-square	*p* value	Chi-square	p value	Chi-square	*p* value
Age	3.90	0.048	0.84	0.359	0.15	0.697	0.01	0.925
Sex	0.25	0.618	0.55	0.457	0.47	0.494	0.11	0.737
Diabetes duration	2.66	0.103	1.22	0.270	0.01	0.937	3.80	0.051
Smoking	0.13	0.720	1.72	0.189	1.84	0.175	2.01	0.157
Use of RAS blockers	0.01	0.930	2.67	0.102	8.63	0.003	0.12	0.733
Coronary heart disease	0.27	0.605	1.85	0.174	0.90	0.342	5.10	0.024
Stroke	0.78	0.378	0.14	0.713	0.04	0.837	0.07	0.796
Retinopathy	0.03	0.860	0.62	0.431	0.62	0.433	0.19	0.663
SBP	0.29	0.590	0.06	0.807	0.79	0.373	0.00	0.966
DBP	1.61	0.204	3.43	0.064	0.48	0.489	6.71	0.010
BMI	0.02	0.900	5.12	0.024	7.62	0.006	34.54	< 0.001
HbA1c	0.19	0.666	4.05	0.044	0.85	0.356	0.91	0.341
Hemoglobin	0.27	0.605	0.47	0.493	0.00	0.980	0.30	0.582
Uric acid	0.00	0.948	8.39	0.004	1.09	0.295	0.57	0.449
LDL cholesterol	0.56	0.454	0.42	0.518	1.43	0.232	0.64	0.425
HDL cholesterol	0.00	0.976	0.07	0.790	1.23	0.267	0.18	0.671
Triglycerides	1.82	0.177	0.10	0.751	0.01	0.941	1.80	0.180

The direction from X to Y indicates that the temporal trend in X, for example age, influences the temporal trend in albuminuria or reduced eGFR during the 10 years more precisely and significantly than only X itself. The direction from Y to X examined the inverse causality

why the prevalence of reduced eGFR recently increased significantly. In our study, however, use of RAS inhibitors was also associated with increased prevalence of albuminuria. These seemingly paradoxical results, frequently observed in observational or cross-sectional studies, may be attributed, at least in part, to reverse causation bias [22] due to the preferential use of RAS inhibitors especially in patients with diabetic nephropathy. Another possibility that use of RAS inhibitors, especially ACE inhibitors, is rather associated with increased risk of progression of nephropathy [23, 24] may not be completely denied.

Beside the use of RAS inhibitors, higher serum levels of uric acid, older age, and lower hemoglobin were significantly associated with reduced kidney function. Hyperuricemia is known to have a bidirectional relationship with chronic kidney diseases including diabetic nephropathy [25, 26]. Renal clearance of uric acid decreases as renal function reduces, resulting in elevation of serum uric acid levels. In addition, hyperuricemia is a well known risk factor for decline in kidney function. We have recently showed that, in Japanese patients with type 2 diabetes and GFR ≥ 60 mL/min/1.73 m^2, higher serum levels of uric acid were significantly associated with increased risk of 30% and 50% reductions in eGFR, as well as progression to end-stage kidney disease [27]. The slightly but significantly increasing trend of serum levels of uric acid in the current study may have contributed to the increase in patients with an eGFR < 60 mL/min/1.73 m^2 over time. The Japanese study showed that age-dependent increase in arterial stiffness was associated with reduced eGFR [13], although independent effects of age and increased stiffness with albuminuria were not determined.

Close associations of higher age and lower levels of hemoglobin or anemia [28, 29] with reduced renal function have been well demonstrated. Most of covariates significantly associated with albuminuria, including presence of retinopathy, lower hemoglobin level [28, 29], greater systolic blood pressure, and higher levels of HbA1c are well known risk factors for development and progression of albuminuria [30–32]. Nonetheless, the fundamental factors associated with the decrease in the prevalence of albuminuria were not clarified in this study.

Finally, the Granger causality test is a unique statistical hypothesis test used to infer whether a time series is useful for predicting another time series [15]. Using this test, we found that changes in the use of RAS inhibitors and BMI showed a significant ability to predict changes over time in the frequency of reduced eGFR. Only the use of RAS inhibitors was consistent with the results of the multivariate logistic regression analysis, strongly suggesting that the recent increase in RAS inhibitor use was closely associated with the increase in patients with reduced kidney function.

The reasons for the discrepancy between the results of the logistic regression analysis and the Granger causality test are unknown but it may be due to the differences in the predictive performance between these statistical analyses.

This study is subject to the attendant limitations. First, the serial cross-sectional study does not allow to assess causal relationships. The Granger causality test was used to complement the limitation, although the test cannot verify close causality, only demonstrating strong associations between two time-series data. Second, while the NHANES and Japanese study covered 27 years [12] and 18 year [13], respectively, our study is based on a shorter (10-year) observation. Third, we studied patients who visited an urban university hospital, likely limiting the generalizability of the results. Fourth, treatment duration of the RAS inhibitors before the study was not assessed. Finally, UACR and serum creatinine were measured on a single occasion, possibly leading to improper categorization of albuminuria and GFR. Nonetheless, we believe this did not affect the temporal trend as this limitation was non-differential throughout the study period.

This study also has strengths. It represents a large single-center study including individuals who were definitely diagnosed as type 2 diabetes by specialist of diabetes. UACR and serum creatinine were measured at a single laboratory, eliminating inter-institutional variance. In addition, we restricted timing of urine collection to first morning, which allowed minimizing the variation of albumin excretion due to exercise and diurnal fluctuations [33].

Conclusions

This large serial cross-sectional study of Japanese patients with type 2 diabetes has shown that the frequency of albuminuria did not change, while the frequency of reduced kidney function increased. However, after adjustment for clinical findings including frequency of the use of RAS inhibitors, a modest but statistically significant decrease in the frequency of albuminuria was observed, whereas the frequency of reduced kidney function remained stable. Taken with the results of the Granger causality test together, changes in clinical and environmental factors may have led to the apparent changes in the renal manifestations over the last decade. The causal nature of the environmental exposures needs to be inferred in future studies, using more sophisticated methods, including Mendelian randomization [34].

Author contributions NT designed the study, collected the data, performed the statistical analyses, researched data, and wrote the manuscript. YYa, YYo, TM, and KH substantially contributed to collection and interpretation of data. TB is the guarantor of this work, had full access to all the data in the study, performed the statistical analyses in part, reviewed/edited the manuscript, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with ethical standards

Conflicts of interest The authors have nothing to declare.

Human rights statement The present study was conducted as a part of the Prospective Cohort Study Elucidating Factors Associated with the Pathogenesis, Prognosis, and Prognosis of Diabetic Nephropathy conducted in Diabetes Center, Tokyo Women's Medical University, the protocol of which was approved by the Ethics Committee of Tokyo Women's Medical University School of Medicine (Approval No. 1584)

Informed consent Since this was an observational but not a prospective intervention study, the Ethics Committee provided a waiver of informed consent.

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