The Prognosis of Patients With Type 2 Diabetes and Nonalbuminuric Diabetic Kidney Disease Is Not Always Poor: Implication of the Effects of Coexisting Macrovascular Complications (JDDM 54)

*Hiroki Yokoyama,[1] Shin-ichi Araki,[2] Koichi Kawai,[3] Katsuya Yamazaki,[3] Shin-ichiro Shirabe,[4] Hidekatsu Sugimoto,[5] Masae Minami,[6] Itsuko Miyazawa,[2] and Hiroshi Maegawa,[2] for the JDDM Study Group**

Diabetes Care 2020;43:1102–1110 | https://doi.org/10.2337/dc19-2049

OBJECTIVE

Nonalbuminuric diabetic kidney disease (DKD) has become the prevailing phenotype in patients with type 2 diabetes. However, it remains unclear whether its prognosis is poorer than that of other DKD phenotypes.

RESEARCH DESIGN AND METHODS

A total of 2,953 Japanese patients with type 2 diabetes and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, enrolled in an observational cohort study in 2004, were followed until 2015. On the basis of albuminuria (>30 mg/g creatinine) and reduced eGFR (<60 mL/min/1.73 m^2) at baseline, participants were classified into the four DKD phenotypes—no-DKD, albuminuric DKD without reduced eGFR, nonalbuminuric DKD with reduced eGFR, and albuminuric DKD with reduced eGFR—to assess the risks of mortality, cardiovascular disease (CVD), and renal function decline.

RESULTS

During the mean follow-up of 9.7 years, 113 patients died and 263 developed CVD. In nonalbuminuric DKD, the risks of death or CVD were not higher than those in no-DKD (adjusted hazard ratio 1.02 [95% CI 0.66, 1.60]) and the annual decline in eGFR was slower than in other DKD phenotypes. The risks of death or CVD in nonalbuminuric DKD without prior CVD were similar to those in no-DKD without prior CVD, whereas the risks in nonalbuminuric DKD with prior CVD as well as other DKD phenotypes were higher.

CONCLUSIONS

Nonalbuminuric DKD did not have a higher risk of mortality, CVD events, or renal function decline than the other DKD phenotypes. In nonalbuminuric DKD, the presence of macrovascular complications may be a main determinant of prognosis rather than the renal phenotype.

[1]*Jiyugaoka Medical Clinic, Internal Medicine, Obihiro, Japan*
[2]*Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan*
[3]*Kawai Clinic, Tsukuba, Japan*
[4]*HEC Science Clinic, Yokohama, Japan*
[5]*Sugimoto Clinic, Kita Kyusyu, Japan*
[6]*Minami Masae Clinic, Fukuoka, Japan*

Corresponding author: Hiroki Yokoyama, dryokoyama@yokoyamanaika.com

Received 15 October 2019 and accepted 25 January 2020

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-2049/-/DC1.

**A complete list of the JDDM Study Group clinics that contributed to this study can be found in the Supplementary Data.*

Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) and a major cause of mortality and cardiovascular disease (CVD) events in patients with type 2 diabetes (1). Increased albuminuria and impaired renal function are the major determinants of DKD. We simply define in this article that the term DKD indicates kidney disease accompanied by diabetes, which is not biopsy-proven kidney disease and thus potentially includes both diabetes and other diseases as the cause of kidney disease. The typical progressive course of DKD is an initial increase in urinary albumin excretion (known as microalbuminuria), progression to macroalbuminuria, and rapid decline in renal function thereafter (1). Thus, albuminuria has traditionally been considered the initial pathway to the progression of decline in renal function (1). However, this has been challenged because many patients with albuminuria have been reported to regress to a normal albumin excretion rate spontaneously or by the comprehensive risk management of DKD (2–6).

Epidemiological studies have indicated that a decreased prevalence of albuminuria and an increased prevalence of a reduced estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2 are the current trend in DKD manifestations. At present, nonalbuminuric renal impairment (i.e., nonalbuminuric DKD) has become the prevailing DKD phenotype in patients with type 1 and type 2 diabetes (7–14). This phenomenon of increasing prevalence of nonalbuminuric DKD may be a result of improving diabetes management, increasing the rate of regression of albuminuria as a consequence of increasing use of renin-angiotensin system (RAS) blockers, and increasing age of the population and/or longevity (15,16). Therefore, it is likely that the diabetic population with nonalbuminuric DKD may further increase in the future.

The lifetime prognosis and progression of CVD and ESRD may differ according to the degree of albuminuria and renal dysfunction. So far, some studies have reported that nonalbuminuric DKD leads to a high risk of mortality (14,17), whereas other studies have indicated conflicting results (18). Although it remains unclear whether the prognosis of nonalbuminuric DKD is different from that of albuminuric DKD, the clinical characteristics of patients with nonalbuminuric DKD appear to be common across ethnicities and are somewhat different from those of albuminuric DKD (7–11,17,18). Patients with nonalbuminuric DKD were older, predominantly female, and had fewer diabetic microvascular complications but more macrovascular complications (7–11,17). These differences suggest that the underlying pathogenesis and determinant factors for their prognosis may differ between nonalbuminuric and albuminuric DKD. In particular, the higher prevalence of macrovascular complications in nonalbuminuric DKD may be associated with the later onset of CVD events and faster decline in renal function. Thus, it is important to carefully investigate the mortality and renal/cardiovascular prognosis according to DKD phenotypes and the presence of macrovascular complications to clarify the underlying pathogenesis and therapeutic strategies to improve the prognosis of patients with DKD.

The aim of this study was to investigate the mortality, CVD events, and renal function decline in patients with type 2 diabetes according to DKD phenotypes. Furthermore, we evaluated the risk in subgroups stratified by the presence of a history of CVD (prior CVD) to specifically assess whether the presence of macrovascular complications influences the prognosis of nonalbuminuric DKD.

RESEARCH DESIGN AND METHODS

Japan Diabetes Clinical Data Management Cohort Study and Participants

The Japan Diabetes Clinical Data Management (JDDM) Study is an ongoing observational prospective cohort study to investigate the impact of risk on CVD morbidity and mortality in individuals with type 2 diabetes (5,7,15). This study group was organized by general practitioners voluntarily gathering from all over Japan to elucidate the status of Japanese diabetes care and promote clinical diabetes research on the basis of daily clinical practice. At baseline, 3,323 Japanese patients with type 2 diabetes and eGFR $\geq$30 mL/min/1.73 m^2, consecutively visiting 17 clinics belonging to this study group in 2004 (see Supplementary Appendix), were eligible. After excluding 370 individuals with missing values or measurements of serum creatinine (Cr) three of fewer times throughout the study period, 2,953 participants were finally analyzed. The daily medical records, such as patient information, clinical data, and medical prescription history, were accumulated at the JDDM central office using common software to collect these data. This primary care setting study is likely to collect the most representative data reflecting the current status of nationwide diabetes care in Japan because there is no national registry system in Japan. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the JDDM-affiliated and locally appointed ethics committees. All participants provided informed consent.

Measurements

Type 2 diabetes was defined by the absence of ketoacidosis and being treated without insulin treatment for at least 2 years after diagnosis, and patients were divided into treatment groups by diet alone, hypoglycemic tablets, or insulin with or without tablets. BMI was calculated as the ratio of body weight (kg) to height squared (m^2). Blood pressure (BP) was measured with an appropriately sized cuff in the sitting position using an automated standardized BP device. Nonfasting blood samples were drawn and analyzed to measure serum Cr and lipids at local laboratories. Glycated hemoglobin A_{1c} (HbA_{1c}) levels were measured at each clinic by high-performance liquid chromatography and presented as National Glycohemoglobin Standardization Program (%) and International Federation of Clinical Chemistry and Laboratory Medicine (mmol/mol) values, according to the recommendations of the Japan Diabetes Society (19). A past medical history of CVD, including myocardial infarction, stroke, foot ulcer/gangrene/amputation, and coronary, carotid, or lower-limb revascularization, was judged on the basis of clinical records confirmed by a medical doctor. Smoking was defined as never, past, or current.

DKD was defined as kidney disease accompanied by diabetes, although the cause of kidney disease was not biopsy proven. DKD was assessed by measuring albuminuria and serum Cr at baseline. Serum and urinary concentrations of Cr and urinary albumin were measured by enzymatic methods and turbidimetric immunoassay, respectively. The urinary albumin excretion rate was recorded as the albumin-to-creatinine ratio (ACR). The GFR was estimated using the following equation by the Japanese Society

of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ × 0.739 (if female). Two or three measurements of ACR and eGFR for each individual were obtained to identify each stage at baseline, and the geometric mean was used for analysis. The ACR values of <30, 30–299, and ≥300 mg/g Cr were considered as normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively. On the basis of albuminuria (ACR <30 or ≥30 mg/g Cr) and eGFR (≥60 or <60 mL/min/1.73 m^2), individuals were classified into the following four DKD phenotypes: no-DKD, albuminuria alone (albuminuric DKD without reduced eGFR), reduced eGFR alone (nonalbuminuric DKD), or albuminuria and reduced eGFR (albuminuric DKD with reduced eGFR).

Follow-up and Outcomes

Patients visited the clinic monthly or bimonthly and were followed up until the end of 2015 or the first occurrence of one of the following end points: nonfatal coronary heart disease (CHD), nonfatal ischemic stroke, peripheral artery disease (PAD), or death. These corresponded to ICD-10 codes I20–21, I63, and I70 (www.who.int/classifications/icd/en/). Definitions of CHD included myocardial infarction, angina pectoris, and coronary interventions. Ischemic stroke included symptomatic brain infarction and carotid revascularization but not silent brain infarction, transient ischemic attack, or brain hemorrhage. PAD was diagnosed when intermittent claudication developed, with the confirmation of an ankle-brachial pressure index <0.9 that was measured automatically by volume plethysmographic apparatus, significant peripheral artery stenosis by angiography, or leg amputation above the ankle as a result of diabetes. The outcomes evaluated in this study were all-cause death, the onset of CVD (i.e., nonfatal CHD, nonfatal ischemic stroke, PAD, or cardiovascular death), the composite of all-cause death and CVD, and the progression of kidney dysfunction. As in the progression of kidney dysfunction, the incidence of the progression to eGFR <30 mL/min/1.73 m^2, the incidence of the progression to eGFR decline ≥30% from the baseline eGFR, and the annual decline rate in eGFR were evaluated. The vital status of study participants on 31 December 2015 and development of CVD during the follow-up period were confirmed by an independent end point adjudication committee, which gathered every 2 years to assess all potential end points and classify them in accordance with predefined criteria as an independent panel.

Statistical Analysis

Continuous data were expressed as the mean ± SD if normally distributed and median (interquartile range) if nonnormally distributed. For comparisons of continuous variables between two groups, unpaired Student *t* test for normally distributed variables or the Mann-Whitney *U* test for nonnormally distributed variables (after first being logarithmically transformed) was used. Comparisons of continuous variables among the four DKD phenotypes were performed by one-way ANOVA. Comparisons between frequencies in the study groups were made by χ^2 tests. Crude mortality rates and crude incidence rates of CVD, composite end points of CVD or death, progression to eGFR <30 mL/min/1.73 m^2, and progression to eGFR decline ≥30% from the baseline eGFR were described as events per 1,000 person-years with the 95% CI. Kaplan-Meier survival probabilities were estimated according to DKD phenotypes, and differences were analyzed by the log-rank test. Comparison of the incidence densities between individuals with prior CVD and those without prior CVD was performed on crude rates using a Mantel-Haenszel method, and the incidence density ratio (relative risk) and 95% CI were calculated. Cox proportional hazards analysis was used to compute the hazard ratio (HR) with 95% CI and cumulative survival rate according to DKD phenotypes using the no-DKD group as a reference, adjusted for baseline age and sex (model 1) or for CVD risk factors and complications/comorbidities at baseline (i.e., age, sex, diabetes duration, BMI, smoking, HbA_{1c}, systolic BP, antihypertensive treatment, HDL and non-HDL cholesterol, lipid-lowering treatment) (model 2). We performed the subanalysis incorporating the use of antihypertensive and lipid-lowering drugs both at baseline and at follow-up, which used the category according to the use at baseline and/or follow-up instead of only baseline use. The analyses were performed on overall individuals and those with or without prior CVD, separately. The annual decline rate in eGFR during the follow-up period was assessed using a linear mixed-effects model with both random intercept and slope terms, and their differences were compared among the four DKD phenotypes. To test the linearity of eGFR trajectories, the difference of mean slope between the former and latter half of the follow-up months was calculated. We considered the difference in slope ≥3 mL/min/1.73 m^2 as nonlinear, according to the definition of nonlinearity by others (20). To create a figure to visualize the trajectories of the annual change in eGFR in subgroups stratified by DKD phenotype, the annual average eGFR measured in each 1-year period in each individual was used as the value of each year. A *P* value of <5% (two-tailed) was considered significant. All analyses were performed using IBM SPSS version 25 (SPSS Japan, Tokyo, Japan) and EZR (21) statistical software packages.

RESULTS

At baseline, the prevalence of DKD phenotypes was 61.1% for no-DKD, 25.3% for albuminuric DKD with preserved eGFR (20.6% with microalbuminuria, 4.7% with macroalbuminuria), 6.9% for nonalbuminuric DKD, and 6.7% for albuminuric DKD with reduced eGFR (3.9% with microalbuminuria, 2.8% with macroalbuminuria) (Table 1). Therefore, one-half (50.6%) of patients with reduced eGFR were normoalbuminuric. Among the four DKD phenotypes, patients with nonalbuminuric DKD were more frequently female, were never-smokers, had lower levels of HbA_{1c} and systolic BP, and had less prevalence of diabetic retinopathy than patients with albuminuric DKD phenotypes. In addition, patients with nonalbuminuric DKD were older than those with no-DKD or albuminuric DKD without reduced eGFR but not different from those with albuminuric DKD with reduced eGFR (Table 1).

During a mean follow-up of 9.7 ± 1.1 years, 2,840 (96.2%) patients were alive, whereas 113 (3.8%) had died; the mortality was 4.0 per 1,000 person-years (95% CI 3.3, 4.7) (Table 2). The crude incidence rate (1,000 person-years) and the cumulative survival rate for death were lowest in no-DKD and highest in albuminuric DKD with reduced eGFR (Table 2 and Supplementary Fig. 1*A*). Compared with no-DKD, the adjusted HRs by the Cox proportional hazards

Table 1—Baseline clinical characteristics of all participants stratified by DKD phenotype

Variable	Overall	Alb^-GFR^- (ACR <30, GFR ≥60)	Alb^+GFR^- (ACR ≥30, GFR ≥60)	Alb^-GFR^+ (ACR <30, GFR <60)	Alb^+GFR^+ (ACR ≥30, GFR <60)	*P*
n (%)	2,953	1,806 (61.1)	746 (25.3)	203 (6.9)	198 (6.7)	
Male (%)	63.7	63.5	66.0	57.1	63.6	NS
Age (years)	58.4 ± 8.3	57.7 ± 8.4	57.9 ± 8.4	62.6 ± 5.8	62.4 ± 6.2	<0.001
Known duration of diabetes (years)	11.0 ± 7.7	10.5 ± 7.6	11.5 ± 7.4	11.7 ± 8.2	13.8 ± 8.4	<0.001
BMI (kg/m^2)	24.7 ± 3.8	24.2 ± 3.4	25.8 ± 4.2	25.0 ± 4.1	25.2 ± 4.0	<0.001
Diabetes treatment (%)						<0.001
Diet	13.4	16.6	7.6	10.3	9.6	
Tablets	65.7	65.4	69.0	67.5	53.5	
Insulin	20.9	18.0	23.3	22.2	36.9	
Smoking history (%)						<0.001
Never	48.2	48.9	44.4	57.6	46.0	
Past	20.6	20.7	18.1	24.6	25.3	
Current	31.2	30.3	37.5	17.7	28.8	
Albuminuria (μg/g Cr)	9.9 (6.3–16.0)	9.9 (6.3–16.0)	87.3 (44.9–226.0)	10.0 (6.4–15.0)	188.0 (64.9–1,000.0)	<0.001
eGFR at baseline (mL/min/1.73 m^2)	78.2 ± 17.7	81.8 ± 14.3	84.1 ± 16.4	53.7 ± 5.4	49.4 ± 7.8	<0.001
HbA_{1c} (%)	7.46 ± 1.07	7.34 ± 0.97	7.81 ± 1.23	7.19 ± 0.89	7.40 ± 1.11	<0.001
HbA_{1c} (mmol/mol)	58.0 ± 11. 7	56.7 ± 10.6	61.8 ± 13.4	55.1 ± 9.7	57.4 ± 12.1	<0.001
Systolic BP (mmHg)	128.6 ± 13.9	126.8 ± 13.8	131.8 ± 13.2	128.2 ± 13.3	133.2 ± 15.5	<0.001
Diastolic BP (mmHg)	74.8 ± 9.2	74.1 ± 9.0	76.3 ± 8.8	74.9 ± 9.2	75.3 ± 10.8	<0.001
Use of antihypertensive drugs (%)						
At baseline	38.0	30.2	46.5	47.8	67.2	<0.001
At follow-up	54.4	47.1	65.1	60.6	73.7	<0.001
Use of RAS inhibitors (%)						
At baseline	25.9	20.2	31.2	33.5	50.5	<0.001
At follow-up	43.4	36.4	53.2	53.7	60.1	<0.001
HDL (mg/dL)	54.8 ± 15.3	55.7 ± 15.3	53.6 ± 14.9	53.6 ± 14.4	52.7 ± 17.3	<0.01
Non-HDL (mg/dL)	144.3 ± 32.3	141.9 ± 30.3	148.1 ± 36.1	146.2 ± 31.3	150.1 ± 33.8	<0.001
Use of lipid-lowering drugs (%)						
At baseline	23.8	21.4	23.7	36.5	33.3	<0.001
At follow-up	39.8	38.5	39.3	48.3	44.9	<0.05
Retinopathy	30.9	23.1	43.7	23.2	62.1	<0.001
History of CVD, *n* (%)	304 (10.3)	134 (7.4)	91 (12.2)	28 (13.8)	51 (25.8)	<0.001
Coronary artery disease	151 (5.1)	65 (3.6)	43 (5.8)	17 (8.4)	26 (13.1)	<0.001
Stroke	140 (4.8)	55 (3.1)	43 (5.9)	15 (7.5)	27 (13.8)	<0.001
PAD	31 (1.1)	13 (0.7)	13 (1.7)	3 (1.5)	2 (1.0)	NS

Data are mean ± SD or median (interquartile range) unless otherwise indicated. ACR is presented in mg/g Cr, and GFR is presented in mL/min/1.73 m^2. Alb^-GFR^-, no-DKD; Alb^+GFR^-, albuminuric DKD without reduced eGFR; Alb^-GFR^+, nonalbuminuric DKD; Alb^+GFR^+, albuminuric DKD with reduced eGFR.

model (model 2) were not significantly different for nonalbuminuric DKD (HR 1.46 [95% CI 0.73, 2.92]) but were significantly higher for albuminuric DKD without reduced eGFR (1.71 [1.09, 2.69]) and albuminuric DKD with reduced eGFR (2.50 [1.39, 4.49]) (Table 2).

During the follow-up, 264 patients developed CVD, yielding the crude incidence rate of 9.5 per 1,000 person-years (95% CI 8.4, 10.7), and 358 patients reached the composite end point of CVD or death, yielding the crude incidence rate of 13.1 per 1,000 person-years (95% CI 11.8, 14.5). The adjusted HRs for CVD and the composite end point of CVD or death compared with those of patients with no-DKD also exhibited similar patterns (i.e., not significantly different for nonalbuminuric DKD but significantly higher for albuminuric DKD without reduced eGFR and albuminuric DKD with reduced eGFR) (Table 2). The subanalysis considering the use of antihypertensive and lipid-lowering drugs both at baseline and at follow-up did not alter the results (data not shown). Moreover, the cumulative survival rates for these outcomes were similar in terms of the differences among the four DKD phenotypes (Fig. 1*A* for the composite, Supplementary Fig. 1*B* for CVD).

Next, we compared the decline in renal function among the DKD phenotypes. The overall incidence rate of progression to eGFR <30 mL/min/1.73 m^2 was 5.7 per 1,000 person-years (95% CI 4.8, 6.7). The incidence rates of progression to eGFR <30 mL/min/1.73 m^2 were the lowest in no-DKD and highest in albuminuric DKD with reduced eGFR (Fig. 1*B* and Table 2). The overall incidence rate of progression to eGFR decline ≥30% was 37.1 per 1,000 person-years (34.6, 39.6). Compared with no-DKD, the fully

Table 2—Crude mortality rates and crude incidences of CVD, composite end point of any CVD or death, and progression to eGFR <30 mL/min/1.73 m^2, with adjusted HRs for each end point and changes in eGFR according to DKD phenotypes

	Overall	Alb$^-$GFR$^-$	Alb$^+$GFR$^-$	Alb$^-$GFR$^+$	Alb$^+$GFR$^+$
n	2,953	1,806	746	203	198
Follow-up period (years), mean ± SD	9.7 ± 1.1	9.8 ± 1.0	8.1 ± 3.4	8.5 ± 3.1	5.7 ± 4.0
Death					
n (%)*	113 (3.8)	51 (2.8)	35 (4.7)	10 (4.9)	17 (8.6)
Incidence per 1,000 person-years (95% CI)	4.0 (3.3, 4.7)	2.9 (2.2, 3.8)	4.8 (2.2, 3.4)	5.1 (2.4, 9.3)	9.1 (5.3, 14.5)
Unadjusted HR (95% CI)		1.0	1.67 (1.09, 2.57)§	1.77 (0.90, 3.48)	3.17 (1.83, 5.48)‡
Adjusted HR (95% CI) in model 1		1.0	1.65 (1.07, 2.53)§	1.34 (0.68, 2.66)	2.33 (1.34, 4.07)‡
Adjusted HR (95% CI) in model 2		1.0	1.71 (1.09, 2.69)§	1.46 (0.73, 2.92)	2.50 (1.39, 4.49)‡
CVD					
n (%)*	264 (8.9)	110 (6.1)	96 (12.9)	17 (8.4)	41 (20.7)
Incidence per 1,000 person-years (95% CI)	9.5 (8.4, 10.7)	6.4 (5.3, 7.7)	14.0 (11.3, 17.0)	8.9 (5.2, 14.2)	24.0 (17.3, 32.4)
Unadjusted HR (95% CI)		1.0	2.19 (1.66, 2.88)†	1.39 (0.83, 2.32)	3.75 (2.62, 5.37)†
Adjusted HR (95% CI) in model 1		1.0	2.14 (1.63, 2.81)†	1.13 (0.68, 1.89)	2.98 (2.08, 4.29)†
Adjusted HR (95% CI) in model 2		1.0	1.75 (1.32, 2.34)†	1.06 (0.63, 1.79)	2.30 (1.57, 3.39)†
Death or CVD					
n (%)*	358 (12.1)	157 (8.7)	125 (16.8)	23 (11.3)	53 (26.8)
Incidence per 1,000 person-years (95% CI)	13.1 (11.8, 14.5)	9.2 (7.8, 10.8)	18.5 (15. 5, 22.0)	12.2 (7.7, 18.2)	32.2 (24.2, 41.9)
Unadjusted HR (95% CI)		1.0	2.01 (1.59, 2.55)†	1.32 (0.85, 2.05)	3.50 (2.56, 4.78)†
Adjusted HR (95% CI) in model 1		1.0	1.97 (1.56, 2.49)†	1.05 (0.68, 1.63)	2.74 (2.00, 3.76)†
Adjusted HR (95% CI) in model 2		1.0	1.73 (1.35, 2.21)†	1.02 (0.66, 1.60)	2.32 (1.67, 3.24)†
Progression to eGFR <30 mL/min/1.73 m^2					
n (%)*	147 (5.0)	10 (0.6)	52 (7.0)	7 (3. 5)	78 (39.4)
Incidence per 1,000 person-years (95% CI)	5.7 (4.8, 6.7)	0.6 (0.3, 1.1)	8.2 (6.1, 10.7)	4.0 (1.6, 8.2)	62.3 (49.5, 77.1)
Unadjusted HR (95% CI)		1.0	13.61 (6.92, 26.78)†	6.53 (2.49, 17.16)†	105.60 (54.63, 204.14)†
Adjusted HR (95% CI) in model 1		1.0	13.48 (6.85, 26.53)†	6.50 (2.46, 17.19)†	105.07 (53.98, 204.52)†
Adjusted HR (95% CI) in model 2		1.0	10.31 (5.18, 20.51)	5.88 (2.21, 15.61)	77.72 (39.32, 153.64)
Progression to eGFR ≥30% decline					
n (%)*	829 (28.1)	336 (18.6)	319 (42.8)	49 (24.1)	125 (63.1)
Incidence per 1,000 person-years (95% CI)	37.1 (34.6, 39.6)	22.7 (20.4, 25.2)	63.4 (56.8, 70.5)	32.0 (23.8, 42.2)	139.4 (117.3, 163.8)
Unadjusted HR (95% CI)		1.0	2.93 (2.51, 3.42)†	1.42 (1.06, 1.92)§	6.22 (5.06, 7.65)†
Adjusted HR (95% CI) in model 1		1.0	2.94 (2.52, 3.42)†	1.30 (0.96, 1.77)	5.77 (4.68, 7.11)†
Adjusted HR (95% CI) in model 2		1.0	2.48 (2.12, 2.91)†	1.25 (0.91, 1.69)	4.62 (3.71, 5.74)†
Annual decline in eGFR (mL/min/1.73 m^2/year) (95% CI)	−1.29 (−1.20, −1.36)	−0.97 (−0.90, −1.04)	−2.17 (−1.95, −2.39)†‖	−0.48 (−0.31, −0.64)†	−2.11 (−1.72, −2.49)†‖
Proportion of nonlinearity (%)*	36.1	34.7	42.3	29.0	33.5

Model 1: adjusted for age and sex. Model 2: model 1 + diabetes duration, BMI, smoking, HbA_{1c}, systolic BP, antihypertensive treatment, HDL and non-HDL cholesterol, and lipid-lowering treatment at baseline. Alb$^-$GFR$^-$, no-DKD; Alb$^+$GFR$^-$, albuminuric DKD without reduced eGFR; Alb$^-$GFR$^+$, nonalbuminuric DKD; Alb$^+$GFR$^+$, albuminuric DKD with reduced eGFR. *$P < 0.001$ by χ^2 test. †$P < 0.001$, ‡$P < 0.01$, §$P < 0.05$ vs. Alb$^-$GFR$^-$. ‖$P < 0.001$ vs. Alb$^-$GFR$^+$.

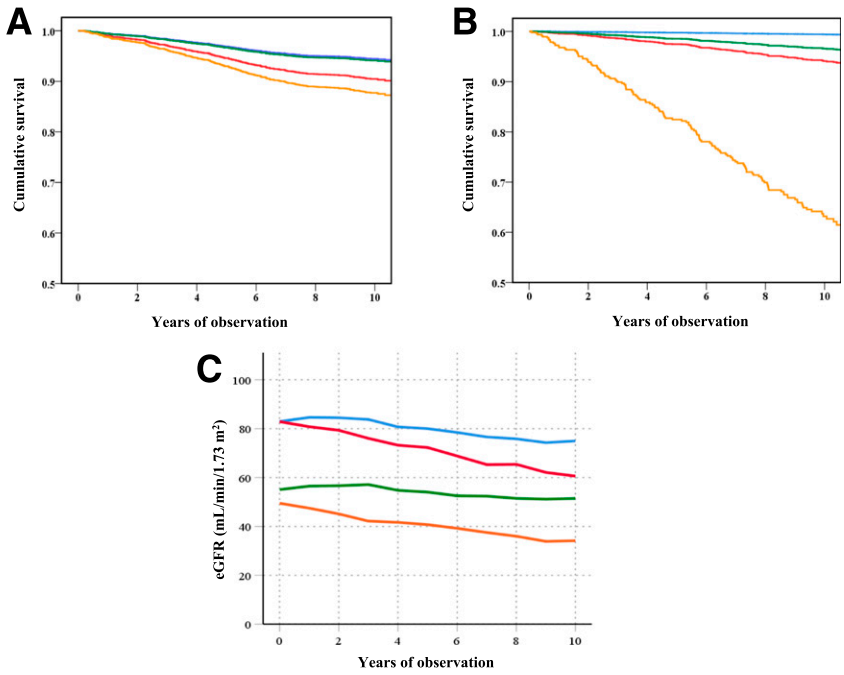

Figure 1—Cumulative survival curves of being free from composite end points of death or CVD (*A*) and from eGFR ≤30 mL/min/1.73 m^2 (*B*) and trajectories of the annual change in eGFR in subgroups stratified by DKD phenotype (*C*). Curves are shown for non-DKD (blue), albuminuric DKD without reduced eGFR (red), nonalbuminuric DKD (green), and albuminuric DKD with reduced eGFR (orange). Cumulative survival curves were obtained by Cox proportional regression analysis adjusted for multiple confounders of model 2 according to DKD phenotypes. The survival curves in (*A* and *B*) across all phenotypes were significantly different by the log-rank test ($P < 0.0001$).

adjusted HR for nonalbuminuric DKD was not significantly different. The eGFR trajectories were linear in most patients (63.9%), whereas the proportion of nonlinearity was smallest for nonalbuminuric DKD (Table 2). The annual decline rate in eGFR, if assuming a linear progression in renal function, was slower in nonalbuminuric DKD than in albuminuric DKD with or without reduced eGFR (Table 2). The eGFR trajectories showed a slower decline in nonalbuminuric DKD compared with that in albuminuric DKD (Fig. 1*C*).

Finally, we investigated the influence of prior CVD on these outcomes (Table 3). Comparison of baseline clinical characteristics between patients with and without prior CVD (Supplementary Table 1) revealed that among patients with nonalbuminuric DKD, those with prior CVD were significantly older with a lower diastolic BP than those without; there were no other significant differences. The risk of death or CVD events in patients with prior CVD was higher than in those without, regardless of DKD phenotype. Of note, the risk of death or CVD events in nonalbuminuric DKD without prior CVD was similar to that in no-DKD without prior CVD, whereas nonalbuminuric DKD with prior CVD had a higher risk than no-DKD without prior CVD as well as other DKD phenotypes. Furthermore, the incidences of both progression to eGFR <30 mL/min/1.73 m^2 and to eGFR ≥30% decline were low in nonalbuminuric DKD without prior CVD.

CONCLUSIONS

This observational study demonstrated that the prognosis in terms of mortality, CVD events, and renal function decline in nonalbuminuric DKD was not poor in comparison with no-DKD in Japanese patients with type 2 diabetes, whereas albuminuric DKD phenotypes exhibited poor prognosis. In particular, nonalbuminuric DKD without prior CVD had a relatively low risk of these outcomes, and its risks were comparable with those in no-DKD without prior CVD. Thus, these results suggest that some of nonalbuminuric DKD represents a distinct phenotype with macroangiopathy instead of microangiopathy as the underlying pathogenesis, which may play a role in the prognosis of CVD events and renal dysfunction. The presence of macrovascular complications may be the main prognostic determinant rather than renal manifestations in nonalbuminuric DKD.

Reduced eGFR and increased albuminuria were reported to be independently associated with an increased risk of death and CVD events in patients with type 2 diabetes (22,23), whereas other studies, including our previous study, reported that nonalbuminuric DKD did not have a high risk of death or CVD events (5,24–26). Our previous 4-year observational study showed that the risk of CVD in patients with type 2 diabetes and without prior CVD (i.e., those with a relatively low risk of CVD) was associated with the progression of albuminuria rather than eGFR stage (5). However, our previous study did not include those with prior CVD and its observation period was relatively short. Thus, in the current study, those with prior CVD were also included and prospectively followed to investigate the impact of past medical history of CVD on the prognosis. As a result, the risk of death and CVD in nonalbuminuric DKD was relatively low compared with that in the other albuminuric DKD phenotypes.

This study confirmed that the risk of death and CVD is higher in patients with diabetes and prior CVD regardless of DKD phenotype. However, nonalbuminuric DKD without prior CVD did not significantly increase the HR for death or CVD in comparison with no-DKD without prior CVD, although other albuminuric DKD without prior CVD had a higher risk. Previous studies found that patients with nonalbuminuric DKD were older, were predominantly female, had relatively lower glycemic control and BP, and had lower co-complicated rates of retinopathy (7–11,17). Our study population had similar clinical features. In particular, these clinical features were observed more in those without prior CVD than in those with prior CVD. Kume et al. (27) recently reported that age-dependent arterial stiffness is associated with reduced eGFR without macroalbuminuria. Taken together, we hypothesize that the underlying pathogenesis in nonalbuminuric DKD mainly comprises two distinct pathogeneses, predominantly macroangiopathy and predominantly microangiopathy, and these underlying pathogeneses may result in different prognoses for CVD and renal function. On the basis of

Table 3—Comparison of incidence of composite end point of any CVD or death and progression to eGFR <30 mL/min/1.73 m^2 between patients with and without baseline CVD, with adjusted HRs for each end point according to DKD phenotypes

	Overall	Alb^-GFR^-	Alb^+GFR^-	Alb^-GFR^+	Alb^+GFR^+
CVD at baseline, *n*					
Without	2,649	1,672	655	175	147
With	304	134	91	28	51
CVD or death					
Incidence of per 1,000 person-years (95% CI)					
Without CVD at baseline	10.7 (9.4, 12.0)	8.1 (6.7, 9.6)	16.4 (13.3, 20. 0)	8.4 (4.6, 14.1)	19.1 (12.4, 28.0)
With CVD at baseline	37.4 (30.3, 45.6)	24.7 (16.6, 35.3)	35.9 (23.8, 51.8)	40.2 (18.5, 74.9)	83.6 (56.3, 118.5)
Relative risk vs. without CVD	3.5 (2. 8, 4.4)	3.1 (2.1, 4.6)	2.2 (1. 4, 3.3)	4. 8 (2.1, 10.9)	4.4 (2.6, 7.4)
Adjusted HR*					
Without CVD at baseline		1.00	1.83 (1.39, 2.41)†	0.85 (0.49, 1.48)	1.73 (1.11, 2.71)§
With CVD at baseline		2.45 (1.62, 3.68)†	2.93 (1.90, 4.51)†	3.16 (1.60, 6.28)‡	5.76 (3.70, 8.97)†
Progression to eGFR <30 mL/min/1.73 m^2					
Incidence per 1,000 person-years (95% CI)					
Without CVD at baseline	4.9 (4.0, 5.8)	0.5 (0.2, 1.0)	8.0 (5.9, 10.7)	1.9 (0.4, 5.7)	6.0 (4.6, 7.7)
With CVD at baseline	13.7 (9.4, 19.2)	1.7 (0.2, 6.1)	9.6 (3.9, 19.6)	18.3 (0.5, 2.6)	70.1 (43.7, 107.0)
Relative risk vs. without CVD	2.8 (1.9, 4.1)	3.3 (0. 9, 15.3)	1.2 (0.5, 2.6)	9.4 (2.1, 41.8)	1.2 (0.7, 1.9)
Adjusted HR*					
Without CVD at baseline		1.00	11.74 (5.47, 25.18)†	3.35 (0.88, 12.75)	94.25 (44.19, 201.01)†
With CVD at baseline		2.71 (0.57, 14.84)†	11.44 (4.06, 32.25)†	28.03 (8.27, 95.03)†	75.76 (31.89, 179.99)†
Progression to eGFR ≥30% decline					
Incidence per 1,000 person-years (95% CI)					
Without CVD at baseline	35.3 (32.8, 37.9)	22.2 (19.8, 24.7)	62.6 (55.7, 70.1)	29.0 (20.7, 39.5)	122.1 (99.9, 147.2)
With CVD at baseline	55.9 (46.2, 67.0)	30.3 (20.5, 43.0)	69.4 (50.1, 93.4)	54.6 (26.5, 98.2)	137.6 (94,8, 190.6)
Relative risk vs. without CVD	1.6 (1.3, 1.9)	1.4 (0.9, 2.0)	1.1 (0.8, 1.5)	1.9 (1.0, 3.7)	1.1 (0.8, 1.7)
Adjusted HR*					
Without CVD at baseline		1.00	2.43 (2.10, 2.88)†	1.16 (0.83, 1.63)	4.94 (3.90, 6.27)†
With CVD at baseline		1.24 (0.85, 1.81)	2.66 (1.90, 3.72)†	2.29 (1.21, 4.33)§	5.15 (3.50, 7.58)†
Annual decline in eGFR (mL/min/1.73 m^2/year) (95% CI)					
Without CVD at baseline	−1.27 (−1.19, −1.35)	−0.97 (−0.90, −1.04)	−2.19 (−1.96, −2.43)‖¶	−0.43 (−0.26, −0.60)‖	−1.98 (−1.53, −2.42)‖¶
With CVD at baseline	−1.36 (−1.08, −1.64)	−0.84 (−0.53, −1.16)	−1.99 (−1.30, −2.67)	−0.79 (−0.27, −1.31)	−2.49 (−1.73, −3.26)‖¶

Alb^-GFR^-, no-DKD; Alb^+GFR^-, albuminuric DKD without reduced eGFR; Alb^-GFR^+, nonalbuminuric DKD; Alb^+GFR^+, albuminuric DKD with reduced eGFR. *HR adjusted for age, sex, diabetes duration, BMI, smoking, HbA_{1c}, systolic BP, antihypertensive treatment, HDL and non-HDL cholesterol, and lipid-lowering treatment (model 2). †$P < 0.001$, ‡$P < 0.01$, §$P < 0.05$ vs. reference group. ‖$P < 0.001$ vs. Alb^-GFR^-. ¶$P < 0.01$ vs. Alb^-GFR^+.

the current study, the prognosis of nonalbuminuric DKD underlying predominantly microangiopathy, which did not have a past medical history of CVD, is not poor. Although the pathogenesis of nonalbuminuric DKD is not fully understood, some studies revealed that patients with nonalbuminuric DKD had fewer typical diabetic morphological changes than those with albuminuric DKD and had a lower risk of renal function decline and all-cause mortality (24,25,28). These results may support our hypothesis.

Penno et al. (17) reported that nonalbuminuric DKD is a strong predictor of mortality. This is not consistent with our present study. One plausible reason for the inconsistent conclusion is a different rate of macrovascular complications. In Japan, the incidence rate of CVD is relatively lower than that in the Caucasian population (29). Indeed, the prevalence of prior CVD in our population was ~10%, which is comparable with that in other Japanese nationwide studies of type 2 diabetes (30). Even in nonalbuminuric DKD, the prevalence of prior CVD was only 13%. On the other hand, in the study by Penno et al., the overall prevalence of prior CVD was 23.1% and of nonalbuminuric DKD, 33.5%. Thus, the prevalence of macrovascular complications in nonalbuminuric DKD may more greatly influence the prognosis than the renal phenotype.

Another possibility may be differences in ethnicity (29). In particular, the differences in clinical characteristics between our population and others, such as lower prevalence of obesity and hypertension, may be important factors. In general, Japanese patients are relatively lean compared with Caucasian patients. The mean BMI and systolic BP in our population were 24.7 kg/m^2 and 128 mmHg, respectively. These are the risk factors for death, CVD events, and renal function decline. Indeed, the overall mortality rate in our population was ~10 times lower than that in a Caucasian study reported by Penno et al. (17).

In addition to the risk for death and CVD events, this study revealed that the renal function decline in nonalbuminuric DKD was comparable with that in no-DKD, consistent with the results of the Chronic Renal Insufficiency Cohort (CRIC) study (18). The CRIC study reported annual rates of eGFR decline in individuals with normoalbuminuria, microalbuminuria, and macroalbuminuria with reduced eGFR of −0.17, −1.35, and −2.74 mL/min/1.73 m^2, respectively, which were comparable to those in our study (data not shown). Thus, our findings are supported by the CRIC study, suggesting that nonalbuminuric DKD has a much lower risk for ESRD or rapid decline in eGFR than other albuminuric DKD phenotypes.

There are some limitations in this study that must be addressed. Our study was designed as an observational follow-up study and not an intervention trial; therefore, we were not able to assess causality. Furthermore, the majority of participants in this study were not confirmed pathologically with renal biopsy. Thus, some with other renal diseases, not diabetes-originated renal disease, may have been included. During the long-term follow-up period, the therapeutic strategy in diabetes management has changed, and several new drugs for diabetes care, including dipeptidyl peptidase 4 inhibitors and sodium–glucose cotransporter 2 inhibitors, were introduced in clinical practice. In addition, the prescription rate of RAS inhibitors increased over the past decade (15). As a result, current diabetes management has markedly improved, and the prevalence of albuminuria is decreasing (12,15). These changes may have reduced the number of patients who progressed to ESRD and developed CVD. Also, these changes may have affected the progression in renal function, resulting in the heterogeneity in eGFR trajectories as nonlinear renal function decline. In this study, we did not perform a time-dependent Cox proportional hazards analysis incorporating these factors over time, although we observed that the increased use of antihypertensive and lipid-lowering drugs at follow-up did not influence the outcomes. Furthermore, we did not evaluate dietary efficacy, such as salt intake, although the Japanese people in general often have a higher salt intake than Caucasians (31). These potential cofounders during the observation period were not evaluated in the current study. Further studies are required to confirm our conclusions.

In conclusion, this observational study demonstrated that Japanese patients with type 2 diabetes and nonalbuminuric DKD have a relatively lower risk of death, CVD events, and renal function decline than those with other albuminuric DKD phenotypes. In particular, the risk of these outcomes in nonalbuminuric DKD without prior CVD was comparable with that in no-DKD without prior CVD, whereas the prognosis in nonalbuminuric DKD with prior CVD as well as other DKD phenotypes with prior CVD was poor. These results suggest that in nonalbuminuric DKD, the presence of macrovascular complications influences the prognosis more than the renal phenotype per se. Further studies are required to clarify which therapeutic strategies are optimal for nonalbuminuric DKD to improve the prognosis.

Acknowledgments. The authors thank Sanae Horiguchi-Watanabe, Risa Sasajima-Yamashita, Suguho Takahashi (Jiyugaoka Medical Clinic), and Daisuke Mutou (JDDM Data Center, Tsukuba, Japan) for skillful data collection and analyses. Dr. H. Obata (National Obihiro Hospital, Obihiro, Japan), Dr. M. Ohtaki (Obihiro Kosei General Hospital, Obihiro, Japan), Prof. H. Sone (Niigata University Faculty of Medicine, Niigata, Japan), and Prof. M. Matsushima (Jikei University School of Medicine, Tokyo, Japan) are thanked as members of the end point adjudication committee.
Funding. This study was supported by the Japan Society for the Promotion of Science KAKENHI grant number JP19K10483 and a research program grant from the Japan Diabetes Society and Manpei Suzuki Diabetes Foundation.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. H.Y. takes responsibility for the statistical method and organizing for performing the multivariate analysis. H.Y., S.A., and I.M. performed the statistical analysis. H.Y., S.A., and H.M. designed the study and drafted the manuscript. H.Y., K.K., K.Y., S.S., H.S., and M.M. generated the data. All authors contributed to the interpretation of the data and critically reviewed the manuscript. H.Y. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Parving HH, Mauer M, Ritz E. Diabetic nephropathy. In *The Kidney*. 8th ed. Brenner BM, Ed. Philadelphia, PA, WB Saunders, 2006, p. 1265–1298
2. de Galan BE, Perkovic V, Ninomiya T, et al.; ADVANCE Collaborative Group. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883–892
3. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309–2320
4. Araki S, Haneda M, Koya D, et al. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes 2007;56:1727–1730

5. Yokoyama H, Araki S, Haneda M, et al.; Japan Diabetes Clinical Data Management Study Group. Chronic kidney disease categories and renal-cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study (JDDM25). Diabetologia 2012;55:1911–1918
6. Yokoyama H, Araki S, Honjo J, et al. Association between remission of macroalbuminuria and preservation of renal function in patients with type 2 diabetes with overt proteinuria. Diabetes Care 2013;36:3227–3233
7. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M; Japan Diabetes Clinical Data Management Study Group. Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrol Dial Transplant 2009;24:1212–1219
8. Penno G, Solini A, Bonora E, et al.; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. J Hypertens 2011;29:1802–1809
9. Pugliese G. Updating the natural history of diabetic nephropathy. Acta Diabetol 2014;51:905–915
10. Thorn LM, Gordin D, Harjutsalo V, et al.; FinnDiane Study Group. The presence and consequence of nonalbuminuric chronic kidney disease in patients with type 1 diabetes. Diabetes Care 2015;38:2128–2133
11. Penno G, Russo E, Garofolo M, et al. Evidence for two distinct phenotypes of chronic kidney disease in individuals with type 1 diabetes mellitus. Diabetologia 2017;60:1102–1113
12. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–2539
13. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
14. Kramer H, Boucher RE, Leehey D, et al. Increasing mortality in adults with diabetes and low estimated glomerular filtration rate in the absence of albuminuria. Diabetes Care 2018;41:775–781
15. Yokoyama H, Araki SI, Kawai K, et al. Declining trends of diabetic nephropathy, retinopathy and neuropathy with improving diabetes care indicators in Japanese patients with type 2 and type 1 diabetes (JDDM 46). BMJ Open Diabetes Res Care 2018;6:e000521
16. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. Kidney Int Suppl (2011) 2018;8(Suppl.):2–7
17. Penno G, Solini A, Orsi E, et al.; Renal Insufficiency And Cardiovascular Events (RIACE) Study Group. Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study. Diabetologia 2018;61:2277–2289
18. Koye DN, Magliano DJ, Reid CM, et al. Risk of progression of nonalbuminuric CKD to end-stage kidney disease in people with diabetes: the CRIC (Chronic Renal Insufficiency Cohort) study. Am J Kidney Dis 2018;72:653–661
19. Seino Y, Nanjo K, Tajima N, et al.; Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010;1:212–228
20. Weldegiorgis M, de Zeeuw D, Li L, et al. Longitudinal estimated GFR trajectories in patients with and without type 2 diabetes and nephropathy. Am J Kidney Dis 2018;71:91–101
21. Fox J. The R commander: a basic statistics graphical user interface to R. J Stat Softw 2005;14:1–42
22. Ninomiya T, Perkovic V, de Galan BE, et al.; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813–1821
23. Drury PL, Ting R, Zannino D, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia 2011;54:32–43
24. Bruno G, Merletti F, Bargero G, et al. Estimated glomerular filtration rate, albuminuria and mortality in type 2 diabetes: the Casale Monferrato study. Diabetologia 2007;50:941–948
25. Rigalleau V, Lasseur C, Raffaitin C, et al. Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care 2007;30:2034–2039
26. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT; PREVEND Study Group. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. Nephrol Dial Transplant 2008;23:3851–3858
27. Kume S, Araki SI, Ugi S, et al. Secular changes in clinical manifestations of kidney disease among Japanese adults with type 2 diabetes from 1996 to 2014. J Diabetes Investig 2019;10:1032–1040
28. Ekinci EI, Jerums G, Skene A, et al. Renal structure in normoalbuminuric and albuminuric patients with type 2 diabetes and impaired renal function. Diabetes Care 2013;36:3620–3626
29. Yokoyama H, Matsushima M, Kawai K, et al.; Japan Diabetes Clinical Data Management Study Group. Low incidence of cardiovascular events in Japanese patients with Type 2 diabetes in primary care settings: a prospective cohort study (JDDM 20). Diabet Med 2011;28:1221–1228
30. Hayashino Y, Izumi K, Okamura S, Nishimura R, Origasa H, Tajima N; JDCP study group. Duration of diabetes and types of diabetes therapy in Japanese patients with type 2 diabetes: the Japan Diabetes Complication and its Prevention prospective study 3 (JDCP study 3). J Diabetes Investig 2017;8:243–249
31. Firestone MJ, Beasley JM, Kwon SC, Ahn J, Trinh-Shevrin C, Yi SS. Asian American dietary sources of sodium and salt behaviors compared with other racial/ethnic groups, NHANES, 2011-2012. Ethn Dis 2017;27:241–248