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Risks for glomerular filtration rate decline in association with progression of albuminuria in type 2 diabetes

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Abstract

Background. The aim of this study was to investigate the annual rate of glomerular filtration rate (GFR) decline and risks for this decline in association with albuminuria progression in type 2 diabetes.

Methods. An observational 4-year cohort study was performed on 1002 subjects with preserved GFR (699 normoalbuminuric), and the predictive value of baseline variables on the GFR slope was investigated. GFR decliner and albuminuria progressor were defined as a GFR slope <-4.0%/year and changes in the geometric mean of urinary albumin from baseline to follow-up >150%, respectively.

Results. Annual rates of GFR decline (percent per year, median and interquartile range) were −2.58 (−4.70 to −0.48) in normoalbuminuria, −3.49 (−5.93 to −1.11) in microalbuminuria and −6.58 (−10.64 to −3.53) in macroalbuminuria. Subjects cross-classified according to GFR decliner/albuminuria progressor consisted of 51% (−/−), 13% (−/+), 28% (+/−) and 8% (+/+). Common risks for GFR decline and albuminuria progression were retinopathy, neuropathy, hemoglobin A_{1C} (HbA_{1C}) and urinary albumin. Independent significant risks for GFR decline were baseline GFR, systolic blood pressure (SBP), total protein (TP) and hypertension. Proportions with progression to albuminuria were similar between GFR decliners and non-decliners. Multiple linear regression analysis indicated that GFR slope was predicted by baseline variables of urinary albumin, GFR, HbA_{1C}, SBP, plasma TP and retinopathy. These risks appeared variable according to high or low levels of urinary albumin and GFR.

Conclusions. Urinary albumin excretion is only one risk factor for albuminuria progression and GFR decline, and other important factors were implicated as important for prevention of end-stage renal disease.

Keywords: albuminuria; glomerular filtration rate; renal disease; type 2 diabetes

Introduction

Development and progression of diabetic nephropathy have been considered according to an increase in urinary albumin excretion followed by progressive decline of the glomerular filtration rate (GFR). However, several reports have recently identified type 2 and type 1 diabetic patients with normoalbuminuria and reduced GFR [1–4]. The UK Prospective Diabetes Study even demonstrated that 51% of patients who progressed to chronic renal failure had no preceding albuminuria (as UKPDS 74) [5]. Reduced GFR is reportedly associated with high cardiovascular morbidity and mortality in the general population [6], as well as in the diabetic population [7]. While albuminuria is a well-known risk factor for cardiovascular disease (CVD) [8], this evidence suggests that not only the progression of albuminuria but also the decline in GFR must be taken into account to prevent end-stage renal disease (ESRD) and cardiovascular events in subjects with type 2 diabetes from the normoalbuminuric stage.

Until recently, studies on renal function loss in type 2 diabetes were performed in subjects with albuminuria, mainly in a small number of subjects by direct measurements of GFR [9, 10]. We reported that slope of GFR decline (percent per year) was significantly steeper in subjects with type 2 diabetes and normoalbuminuria (median −2.39) than in those without type 2 diabetes (median −1.02) [11]. Prevention of ESRD needs studies on subjects with preserved renal function including a wide range of urinary albumin excretion. However, there are few studies that have investigated determinants of GFR decline in type 2 diabetes including normo-, micro- and macroalbuminuria. We performed multiple measurements of estimated GFR over time in a large number of subjects with type 2 diabetes and preserved GFR. This observational cohort study explored the rate of GFR decline in type 2 diabetes with normo- micro-, and macroalbuminuria, the factors associated uniquely and/or commonly with GFR decline and albuminuria progression and the determinants relating to annual rate of GFR decline. The aim of the study was to investigate risk factors for GFR decline to prevent ESRD in type 2 diabetes in association with the status of urinary albumin excretion rate.

Patients and methods

Study population

An observational cohort study was performed. All consecutive patients with type 2 diabetes who visited the outpatient clinic of Jiyugaoka Internal Medicine were enrolled between 2004 and 2006. Individuals who had already been treated for diabetes or hypertension were included in the study in 2004. In order to avoid acute effects of lowering blood glucose and blood pressure (BP) on the GFR slope, individuals whose treatments for diabetes and/or hypertension were newly started were included in the study after five visits, for at least >3 months, when their BP control and/or blood glucose control were stabilized. All subjects that fulfilled the following inclusion and exclusion criteria participated in the study. Individuals who attended the clinic for >1 year, had more than three measurements of serum creatinine after 2004 and had three measurements of the urinary albumin to creatinine ratio (ACR) at baseline and at follow-up were eligible for inclusion. Patients with a serum concentration of creatinine of >132.6 μmol/L were not included. Subjects were followed up to 2008. The study was approved by the local ethical committee and was carried out in accordance with the Helsinki Declaration II.

Type 2 diabetes was diagnosed according to the Japan Diabetes Society (JDS) criteria [12]. Hypertension was defined by a systolic blood pressure (SBP) of >140 mmHg or diastolic blood pressure >90 mmHg, or both, or patients already being treated with antihypertensive drugs. Hyperlipidemia was defined as serum concentrations of total cholesterol of >5.7 mmol/L, triglycerides (TG) of >1.7 mmol/L or high-density lipoprotein (HDL) cholesterol of <1.0 mmol/L or patients already being treated by lipid-lowering agents. Low-density lipoprotein cholesterol level was calculated by Friedewald's formula. Diabetic retinopathy was diagnosed after pupillary dilation by ophthalmologists. Neuropathy was diagnosed in patients with two or more of the following three features: presence of symptoms, absence of ankle tendon reflexes and abnormal scores of vibration perception threshold using a C128 tuning fork, where bilateral spontaneous pain, hypoesthesia and paresthesia of the legs were considered to be neuropathic symptoms.

Measurements

BP was measured with an appropriately sized cuff in the sitting position after resting for >5 min. Three measurements on different days were recorded, and the average was used for the analysis. Non-fasting blood samples were obtained for measurements of glycosylated hemoglobin A_{1C} (HbA_{1C}), plasma concentrations of glucose and total protein (TP), serum concentrations of creatinine and lipids and blood cell counts at the baseline and at 1-year follow-up. HbA_{1C} was measured by high-performance liquid chromatography (normal range 4.3–5.8%) and was certified by the American National Glycohemoglobin Standardization Program (NGSP = 1.019 × JDS + 0.30). Serum and urinary concentrations of creatinine were measured by an enzymatic method with an isotope-dilution mass spectrometry traceable calibrator (N-assay L Creatinine Kit; Nittoubo Medical Co., Tokyo, Japan). The method was consistent throughout the study period with interassay variation coefficients of 0.38 and 0.43% at creatinine concentrations of 91.1 and 362.4 μmol/L, respectively. Urinary albumin was measured by a turbidimetric immunoassay. The urinary albumin excretion rate (AER) was measured using the ACR in random urine samples. Normoalbuminuria, microalbuminuria and macroalbuminuria were defined as an ACR <3.5 mg/mmol, ACR 3.5 and <35.0 mg/mmol and ACR 300 mg/gcr, respectively, in at least two of three consecutive samples. The geometric mean from three samples, obtained at both baseline year and the last year, was used as a continuous variable. The GFR was estimated using the following equation recently generated by The Japanese Society of Nephrology: GFR (mL/min/1.73 m^2) = 194 × $Scr^{-1.094}$ × $Age^{-0.287}$ × 0.739 (if female) [13]. The new Japanese equation is reasonably accurate in estimating GFR for the Japanese population and is more accurate than the modified Modification of Diet in Renal Disease equation refitted for the Japanese by overcoming the underestimation of GFR at high values up to 110 mL/min/1.73 m^2 [13]. Serum concentration of creatinine was measured every 4–6 months in each individual. The first two values of GFR from the entry into the study were recorded and the average was used as the baseline GFR value considering the physiological variations for serum creatinine concentrations.

Statistical analysis

For each subject, a linear regression model of time on GFR (least squares method) was created, and the slope of the regression line was used to estimate the subject's change in GFR over time. Then the GFR slope was expressed as percent per year by dividing the slope by the baseline GFR value. The GFR decliner was defined as GFR slope <−4.0%/year, which was obtained from the control subjects aged 50–70 years in the Baltimore Aging Study [14] and was recently used elsewhere [11]. The albuminuria progressor was defined as changes in the geometric mean in ACR from baseline to follow-up >150%. Results are given as the mean ± standard deviation unless otherwise stated. The significance of differences between the two groups was determined by chi-squared tests for categorical variables and the unpaired Student's *t*-test for continuous variables. Multiple linear regression was used to analyze the associations of variables with GFR slope values (or baseline GFR values), controlling for potential confounders. P-values <5% (two-tailed) were considered significant. All analyses were performed with the statistical software package Dr. SPSS II (SPSS Japan Inc., Tokyo, Japan).

Table 1. Clinical characteristics of subjects with type 2 diabetes at baseline and follow-up (DBP, diastolic blood pressure; LDL, low-density lipoprotein; RASI, renin–angiotensin system inhibitor)

		Baseline urinary albumin status		
	All subjects	Normoalbuminuria	Albuminuria	P-value
n	1002	699	303	
Male (%)	687 (68.6)	485 (69.4)	164 (65.9)	
Age (years)	59 ± 12	58 ± 12	60 ± 12	0.0280
BMI (kg/m^2)	26.0 ± 4.2	25.7 ± 4.1	26.5 ± 4.4	0.0043
Duration of diabetes (years)[a]	6 (2 to 12)	5 (2 to 11)	7 (3 to 14)	0.0001
Diet/tablet/insulin (%)	16.1/64.8/19.2	17.7/66.4/15.9	12.2/61.1/26.7	0.0001
HbA_{1C} (%)				
At baseline	6.7 ± 1.1	6.6 ± 1.0	7.0 ± 1.2	0.0001
At end of follow-up	6.8 ± 1.0	6.7 ± 0.9	7.0 ± 1.2	0.0001
ACR (mg/mmol)[a]				
At baseline	2.0 (1.1 to 4.2)	1.4 (0.9 to 2.1)	8.3 (4.8 to 20.3)	0.0001
At end of follow-up	1.6 (0.9 to 4.2)	1.2 (0.8 to 2.0)	6.9 (2.9 to 23.7)	0.0001
Retinopathy (%)				
At baseline	22.9	17.6	35.3	0.0001
At end of follow-up	25.8	19.1	41.2	0.0001
Neuropathy (%)				
At baseline	26.4	23.6	33.0	0.0025
At end of follow-up	30.4	26.4	39.9	0.0001
Serum creatinine (μmol/L)				
At baseline	67.2 ± 18.6	66.3 ± 17.7	70.7 ± 21.2	0.0001
At end of follow-up	76.0 ± 30.1	71.6 ± 19.4	84.9 ± 45.1	0.0001
GFR (mL/min/1.73 m^2)[b]				
At baseline	77.8 (65.8 to 90.9)	78.7 (68.2 to 90.7)	76.2 (56.9 to 91.9)	0.007
At end of follow-up	70.0 (57.8 to 82.6)	71.7 (61.2 to 82.9)	62.6 (49.2 to 80.8)	0.0001
Change (follow-up minus baseline)	−7.7 (−14.4 to −1.7)	−7.1 (−13.1 to −1.3)	−9.2 (−16.7 to −2.6)	0.0001
GFR slope (%/year)[b]	−2.89 (−5.21 to −0.69)	−2.58 (−4.70 to −0.48)	−3.85 (−6.68 to −1.35)	0.0001
Hypertension (%)	55.8	51.8	65.0	0.0001
SBP (mmHg)				
At baseline	126 ± 15	124 ± 14	130 ± 16	0.0001
At end of follow-up	123 ± 15	122 ± 15	125 ± 15	0.0074
DBP (mmHg)				
At baseline	69 ± 11	68 ± 11	69 ± 11	0.1804
At end of follow-up	67 ± 11	67 ± 11	66 ± 11	0.0080
Antihypertensive user				
At baseline	48.6	46.9	61.1	0.0001
At end of follow-up	60.9	55.2	73.9	0.0001
RASI user in subjects with hypertension (%)				
At baseline	77.3	76.2	79.2	0.4914
At end of follow-up	85.3	84.5	86.8	0.5584
Dyslipidemia (%)	69.8	66.8	76.8	0.0026
HDL-cholesterol (mmol/L)	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	0.0106
LDL-cholesterol (mmol/L)	2.8 ± 0.8	2.8 ± 0.8	2.9 ± 0.8	0.0728
Triglycerides (mmol/L)	1.6 (1.1 to 2.2)	1.5 (1.0 to 2.1)	1.7 (1.2 to 2.6)	0.0003
Statin user				
At baseline	19.0	18.0	21.1	0.3726
At end of follow-up	31.2	32.1	29.3	0.5039
Plasma TP (g/L)				
At baseline	71.6 ± 6.3	71.2 ± 6.2	72.6 ± 6.4	0.0011
At end of follow-up	71.7 ± 4.4	71.4 ± 4.3	72.3 ± 4.8	0.0041
Hemoglobin (g/dL)	14.0 ± 1.5	14.1 ± 1.5	13.9 ± 1.5	0.1881
Platelet (10^4/mm^3)	22.4 ± 5.9	22.5 ± 5.8	22.1 ± 6.1	0.3391
Length of follow-up (years)[a]	3.8 (2.9 to 4.3)	3.8 (3.0 to 4.3)	3.6 (2.9 to 4.3)	0.0845
Number of creatinine measurements[a]	9 (7 to 10)	9 (7 to 10)	9 (7 to 11)	0.2746
Number of ACR measurements[a]	11 (8 to 13)	11 (8 to 13)	11 (8 to 13)	0.5555

[a]Median and interquartile range are given.
[b]Median and interquartile range are given.

Results

Nephropathy stages and subsequent rate of GFR decline

Among all subjects with type 2 diabetes enrolled in the study (n = 1002), 699 had normoalbuminuria and 303 had albuminuria (microalbuminuria 249, macroalbuminuria 54). The median follow-up time was 3.8 years with a median number of nine GFR measurements per subject. Clinical characteristics of the subjects at the baseline and follow-up are shown in Table 1. At the baseline, subjects with albuminuria were more likely to have retinopathy, neuropathy,

Table 2. Comparison of clinical variables according to the cross-classification by presence or absence of GFR decline and presence or absence of albuminuria progression (DBP, diastolic blood pressure; RASI, renin–angiotensin system inhibitor); nonsignificant variables both for GFR decline and for albuminuria progression were not shown; stage progressor and regressor indicate subjects who changed from normoalbuminuria to albuminuria and from micro/macroalbuminuria to normo/microalbuminuria, respectively.

GFR decline Urinary albumin progression *n* (%)	(−) (−) 512 (51.1)	(−) (+) 128 (12.8)	(+) (−) 286 (28.5)	(+) (+) 76 (7.6)	P-values between GFR decline (+) and (−)	P-values between urinary albumin progression (+) and (−)
Male (%)	70.7	69.5	62.2	76.3	0.0472	0.2624
HbA_{1C} (%)						
At baseline	6.55 ± 0.90	6.80 ± 1.19	6.98 ± 1.15	7.05 ± 1.23	0.0001	0.0210
At end of follow-up	6.37 ± 0.88	7.07 ± 1.54	6.52 ± 0.95	6.87 ± 1.15	0.2326	0.0001
ACR (mg/mmol)[a]						
At baseline	1.5 (1.0–3.1)	2.4 (1.2–4.7)	2.5 (1.4–6.3)	2.9 (1.5–21.7)	0.0001	0.0002
Normo/micro/macro (*n*)	399/103/10	83/40/5	176/86/24	41/20/15	0.0001	0.0010
At end of follow-up	1.2 (0.8–2.2)	6.4 (3.2–17.2)	1.5 (0.9–3.3)	9.9 (3.6–77.5)	0.0001	0.0001
Stage progressor (*n*)	6 of 399	47 of 83	2 of 176	22 of 41	0.9999	0.0001
Stage regressor (*n*)	54 of 113	0 of 45	51 of 110	0 of 35	0.9513	0.0001
Retinopathy (%)	14.1	23.4	49.5	42.1	0.0001	0.0062
Neuropathy (%)	18.6	34.4	33.2	40.8	0.0001	0.0003
GFR (mL/min/1.73 m^2)						
At baseline	78.3 ± 19.4	73.6 ± 18.9	80.8 ± 22.8	83.3 ± 24.9	0.0179	0.2306
At end of follow-up	74.8 ± 18.7	70.5 ± 19.9	64.0 ± 19.2	63.4 ± 23.8	0.0001	0.0484
Change (follow-up minus baseline)	−3.5 ± 7.6	−3.2 ± 8.6	−16.8 ± 9.9	−19.9 ± 10.9	0.0001	0.1821
Hypertension (%)	49.0	59.4	64.3	63.2	0.0001	0.1258
SBP (mmHg)	125 ± 14	124 ± 14	129 ± 15	126 ± 18	0.0001	0.7908
HDL (mmol/L)	1.4 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	0.3871	0.0003
TG (mmol/L)	1.8 ± 1.3	2.2 ± 2.7	1.9 ± 1.3	2.2 ± 1.7	0.1757	0.0041
Plasma TP (g/L)	71.9 ± 5.5	72.2 ± 6.2	70.7 ± 7.2	71.7 ± 7.3	0.0012	0.2493

[a]Median and interquartile range are given.

Table 3. Results of multiple linear regression analysis to assess the significance of baseline variables on GFR slope in all subjects and in subgroups according to the levels of baseline urinary albumin and GFR[a]

			Baseline urinary albumin status				Baseline GFR status			
	All subjects		Normoalbuminuria		Albuminuria		High GFR		Low GFR	
	RC (0.19)	P	RC (0.12)	P	RC (0.26)	P	RC (0.19)	P	RC (0.22)	P
Baseline urinary albumin, per log(ACR)	***−1.924***	***0.000***	−1.126	0.118	***−2.418***	***0.002***	***−1.424***	***0.001***	***−2.609***	***0.000***
Baseline GFR, per 10 mL/min/1.73 m^2	***−0.519***	***0.000***	***−0.600***	***0.000***	***−0.478***	***0.004***	−0.210	0.142	***−1.054***	***0.000***
Baseline HbA_{1C}, per %	***−0.486***	***0.001***	***−0.423***	***0.010***	−0.431	0.180	***−0.690***	***0.000***	−0.284	0.258
Baseline SBP, per 10 mmHg	***−0.349***	***0.001***	***−0.351***	***0.003***	−0.334	0.131	***−0.358***	***0.020***	***−0.323***	***0.029***
Baseline plasma TP, per g/L	***0.161***	***0.000***	***0.086***	***0.001***	***0.302***	***0.000***	***0.207***	***0.000***	***0.125***	***0.000***
Retinopathy	***−1.232***	***0.001***	***−1.006***	***0.017***	−1.302	0.108	***−1.798***	***0.001***	***−1.121***	***0.038***

[a]The independent variables were baseline factors such as age, BMI, gender, HbA_{1C}, retinopathy, neuropathy, SBP, RASI use, baseline GFR, baseline urinary albumin, serum concentrations of HDL, low-density lipoprotein and TG, plasma TP, hemoglobin and platelets. High GFR included subjects with GFR greater than the median GFR of 77.9. Regression coefficient (RC) means milliliter of change in GFR by units of change in the risk factors. Numbers in parentheses indicate the R^2 value.
The bold/italic values indicate significant associations with GFR slope.

hypertension and dyslipidemia and to have higher values of body mass index (BMI), duration of diabetes, HbA_{1C}, SBP and TG but lower values of GFR and HDL-cholesterol than those with normoalbuminuria. Proportion of subjects with GFR >60 mL/min/1.73 m^2 was 82.4% at baseline and 71.4% at follow-up. The GFR slope (percent per year) was significantly steeper in subjects with albuminuria than in those with normoalbuminuria, and it was steeper in subjects with macroalbuminuria [median and interquartile range −6.58 (−10.64 to −3.53)] than in those with microalbuminuria [−3.49 (−5.93 to −1.11)] ($P < 0.0001$).

Factors associated with GFR decline and/or albuminuria progression

When subjects were cross-classified according to the presence or absence of GFR decline and the presence or absence of urinary albumin progression, 51.1% were without

GFR decline and without urinary albumin progression, whereas 7.6% exhibited GFR decline with urinary albumin progression (Table 2). Those with GFR decline were more likely to be female and to have retinopathy, neuropathy, hypertension, higher values of HbA_{1C}, urinary albumin, GFR and SBP and lower TP values than those without GFR decline. Those with urinary albumin progression were more likely to have retinopathy, neuropathy and higher baseline values of HbA_{1C}, urinary albumin, TG and low HDL values than those without urinary albumin progression. The proportion of subjects with normoalbuminuria who developed albuminuria was 11.1% (24/217) in those with GFR decline, which was similar to the 11.0% (53/482) in those without GFR decline ($P = 0.99$). The proportion of subjects with micro/macroalbuminuria who regressed to normo/microalbuminuria was 35.2% (51/145) in those with GFR decline, which was similar to the 34.2% (54/158) in those without GFR decline ($P = 0.95$).

Variables relating to annual rate of GFR decline by multiple linear regression analysis

In multiple linear regression analysis with the GFR slope (percent per year) as the dependent variable and baseline factors described in Table 3 as the independent variables, only the significant variables were shown. The GFR slope was significantly and independently predicted by the higher baseline values of urinary albumin, GFR, HbA_{1C}, SBP and lower plasma TP and the presence of retinopathy in all subjects. For example, baseline SBP of 140 mmHg instead of 130 mmHg accelerated -0.349 mL/min/1.73 m^2 in annual rate of GFR decline. Subgroup analyses according to normoalbuminuria/albuminuria indicated that high GFR and low TP significantly affected subsequent GFR decline in both normoalbuminuric and albuminuric subjects. High HbA_{1C}, high SBP and retinopathy were predictors of GFR decline only in subjects with normoalbuminuria, and high urinary albumin was a predictor of GFR decline only in subjects with albuminuria. Subgroup analyses according to high/low levels of baseline GFR indicated that urinary albumin, SBP, plasma TP and retinopathy were significant predictors of GFR decline in both high and low GFR groups. High HbA_{1C} was associated with GFR decline only in the high GFR group, and high baseline GFR was associated only in the low GFR group.

Discussion

In this study, we confirmed risk factors for GFR decline to be high HbA_{1C} [15, 16], high GFR [17], high BP [18], high urinary albumin [16, 19, 20] and low plasma TP (or serum albumin) [21, 22]. Furthermore, we found that the presence of microangiopathy was significantly associated with a greater GFR decline. While most previous studies referred to subjects with poorly controlled HbA_{1C} [15, 16] and SBP [15, 16, 18] and with type 1 diabetes [20] and altered albuminuria (i.e. diabetic nephropathy) [18, 21], this observational cohort study examined the GFR slope in subjects including a large number of subjects with type 2 diabetes and preserved GFR who had been stabilized and well controlled for metabolic and BP profiles.

Annual rate of GFR decline according to nephropathy stages

Albuminuria is a well-known risk factor for developing ESRD and GFR decline, however, there is little information concerning the concrete annual rate of GFR decline analyzed in each stage of diabetic nephropathy, namely, normoalbuminuria, microalbuminuria and macroalbuminuria. Recently, a method for serum creatinine concentration has been changed from Jaffe's method to enzymatic method and the validity of estimated GFR using this enzymatic method has facilitated the calculation of concrete rate GFR decline based on the multiple data of GFR [13]. The rate of GFR decline in each stage is in accordance with data recently reported by Babazono *et al.* [19]. Compared with normoalbuminuria, annual rate of GFR decline is 1.35-fold higher in microalbuminuria and 2.55 fold higher in macroalbuminuria, which was firmly supported by Babazono *et al.* [19].

Common and independent factors predictive of GFR decline and albuminuria progression

UKPDS 74 also investigated common and independent factors predictive of the development of renal impairment and albuminuria in type 2 diabetes [5], where baseline urinary albumin was predictive for both outcomes, which was similar to our result. The end point in their study was a single category, namely, development of albuminuria and renal impairment. Our study design was distinct from UKPDS 74 in that we examined both GFR decline as a category and GFR slope as a continuous value, which were obtained by multiple data of GFR over time and should be more sensitive to detect risk predictors. Ethnicity, baseline duration of diabetes and levels of urinary albumin, follow-up period and values of BMI and BP were different between the two studies, which may yield consistent and inconsistent findings. UKPDS 74 was different from our study in that both poor metabolic control and high GFR (i.e. low serum creatinine) were not predictive of renal impairment. Adverse effects of poor metabolic control on renal function loss have been reported in other studies on Caucasian type 2 diabetes [15, 16], which is consistent with our study. However, the adverse effect of high GFR on renal function loss remains controversial. Some studies indicate that high GFR is a risk factor for subsequent GFR decline [17] and some do not [5, 18, 23]; thus, further studies are necessary. It is likely that poor metabolic control enhances GFR and leads to a greater GFR decline [11] since many reports support an association of hyperglycemia with elevated GFR [24, 25], and hyperglycemia-induced increased nitric oxide generation leading to glomerular hyperfiltration has been demonstrated [26, 27]. On the other hand, the effect of HbA_{1C} on GFR decline was abolished in subjects with albuminuria and low GFR, which is consistent with other studies [9, 21], and may emphasize the importance of intensive metabolic control from the early stages of diabetes.

Our study showed that albuminuria is one, not fully explainable, risk factor for the GFR decline in subjects with preserved GFR and a wide range of AER. This supports the notion that a decline in GFR precedes the onset of microalbuminuria [1–5]. Perkins *et al.* [28] indicated in the study

of a small number of subjects with type 1 diabetes and new-onset microalbuminuria that one-third developed advanced chronic kidney disease (CKD) soon after the onset of microalbuminuria and that this was not conditional on the presence of macroalbuminuria. We agree with a concept that the pathogenetic mechanisms leading to the development of increased albuminuria and impaired renal function may differ, in which the former is closely related to diabetic glomerulopathy and the latter to tubulointerstitial lesions [29].

We found that the rates of development of microalbuminuria and of regression of albuminuria were not different between GFR decliners and non-decliners. Overall, progression and regression rates of albuminuria stages, 11 and 35% during the 4 years in our study, were comparable to other studies or even better [30–32]. The extensive use of renin–angiotensin system inhibitors may have resulted in this observed finding, including achievement of better BP control than the other previous studies [15–18, 30, 31]. SBP was a risk for GFR decline but not for albuminuria progression under the strict BP control in this study, indicating that GFR decline might be more vulnerable to the deleterious effect of SBP than albuminuria progression. The underlying mechanism may be that SBP plays a crucial role in glomerular pressure and glomerular filtration leading to glomerular damage and renal function loss [33].

Interestingly, Appel *et al.* [34] indicated no effect of intensive BP control in nondiabetic hypertensive CKD with a mean GFR of ~47 mL/min/1.73 m^2. The beneficial effect was considered in proteinuric patients, while the effect was not significant when the outcomes were confined to kidney disease (a doubling of the serum creatinine or ESRD) after subtraction of death from the primary outcome. In our subjects with a mean GFR of ~76.0 mL/min/1.73 m^2 and normoalbuminuria, baseline BP had a beneficial effect on retarding renal function loss. The effect was not observed in albuminuric subjects. We presume that in the diabetic population the case is different and treatment with modifiable hemodynamic and metabolic factors appears beneficial in the subjects with less complication.

Study limitations

Some limitations of the current study need to be mentioned. The threshold for albuminuria progression is open to debate. AER, assessed as a continuous variable, is extremely important since AER values have been shown quite worthy of consideration, both within the low normoalbuminuric range and within the albuminuric range [8, 19, 31]. On the basis of the 30–40% coefficient of variation in AER, we estimated the geometric mean of three measurements at baseline and follow-up. In proteinuric (macroalbuminuric) range, not only the level itself but also the decrease and/or increase were associated with subsequent kidney function loss and CVD occurrence [8, 21]. Since the increase in AER is not linear and a threshold of 50% reduction was shown to be beneficial for renal and cardiovascular risk reduction as so-called 'regression' in previous studies [8, 31], we set 150% increase as 'progression'. Using the threshold of <-4.0%/year for GFR decline, the proportion of those with decline in individuals without diabetes was 27% [11]. Although this is arbitrary and needs a large number of healthy controls with a long follow-up for determination, incorporation of the slope strengthens the validity of this study. In addition, a longer observation period up to the onset of ESRD may be conclusive in terms of evaluating the GFR decline. However, GFR values and the risks during the follow-up are important, and our findings revealed multiple clinical factors related to the slope of GFR decline from various aspects.

In conclusion, the slope of GFR decline was predicted by multiple factors such as baseline values of urinary albumin, GFR, HbA_{1C}, SBP and retinopathy. There are common and independent risk factors predictive of GFR decline and albuminuria progression in type 2 diabetes. Improved prediction of ESRD was recently indicated through the combination of GFR and albuminuria to classify CKD in a general health study [35], and our study highlights the value of multifactorial intervention that focuses on multiple predictive risks found in the study, and this may be of help in prevention of GFR decline and albuminuria progression.

Conflict of interest statement. None declared.

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