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Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15)

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Abstract

Background. Microalbuminuria is widely accepted as the first clinical sign of diabetic nephropathy. However, normoalbuminuric type 2 diabetic patients who have renal insufficiency (RI), i.e. low estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, exist. We explored the prevalence of such patients and associated clinical factors.
Methods. We investigated the distribution of patients when stratified by albuminuria stages and chronic kidney disease (CKD) stages in a large-scale population of Japanese type 2 diabetic patients ($N = 3297$), and the common and independent factors for albuminuria and low eGFR.
Results. The proportion of subjects with low eGFR was 15.3% (506/3297), which was 11.4% among those with normoalbuminuria (NA) (262/2298), 14.9% among those with microalbuminuria (105/705) and 47.3% among those with macroalbuminuria (139/294). There were 262 patients with NA and low eGFR, and 63.4% of them had neither diabetic retinopathy nor neuropathy. They were older and included a higher proportion of women and patients with hypertension, hyperlipidaemia and cardiovascular disease (CVD), and fewer smokers compared with those with NA and preserved eGFR. Multiple logistic regression analysis revealed that factors commonly associated with RI and albuminuria were hypertension, CVD and proliferative retinopathy. Factors independently associated with RI were age, duration of diabetes, A1C (negative), hyperlipidaemia, smoking (negative) and macroalbuminuria, whereas those associated with albuminuria were male sex, BMI, A1C, simple retinopathy and RI.
Conclusions. A significant proportion of type 2 diabetic patients have normoalbuminuric RI. Renal disease in type 2 diabetes could be heterogeneous, implying the possibility of involvement of renal atherosclerosis and lipid toxicity.

Keywords: chronic kidney disease; glomerular filtration rate; normoalbuminuria; renal insufficiency; type 2 diabetes

Introduction

The development of microalbuminuria has been considered to be one of the first clinical signs of a classic course of diabetic nephropathy, which leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR) and eventually end-stage renal disease. These steps

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were originally described in type 1 diabetes [1], whereas kidney disease in type 2 diabetes is more heterogeneous. Several reports have recently identified type 2 and type 1 diabetic patients with normoalbuminuria and low GFR [2–8]. The UK Prospective Diabetes Study even demonstrated that 51% of patients who progressed to chronic renal failure had no preceding albuminuria [9]. However, the proportions of patients with low GFR among type 2 diabetic patients with normoalbuminuria, microalbuminuria or macroalbuminuria remain uncertain, and few such data are available on Asian diabetic populations. Therefore, the clinical features of type 2 diabetic patients with normoalbuminuria and reduced GFR need to be clarified. Clinical factors associated with albuminuria and low GFR may be common but could be independent.

The estimated GFR (eGFR) using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study has been suggested as the best validated means for transforming serum creatinine measurements into GFR in adults, using age, sex and ethnicity as surrogates for muscle mass [10–12]. Stages of chronic kidney disease (CKD) have been proposed by the Kidney Disease Outcomes Quality Initiative guidelines [13] according to the eGFR.

In this study with a large-scale population of Japanese type 2 diabetes, we investigated (1) the distribution of patients when stratified by albuminuria stages and CKD stages and (2) which clinical factors are common and independent for albuminuria and low eGFR.

Patients and methods

Study population

A multicentre study was conducted. It encompassed 17 medical clinics (i.e. general practitioners) or general/university-affiliated hospitals from different areas in Japan, using the same software to incorporate patient records, as a working study group, i.e. the Japan Diabetes Clinical Data Management (JDDM) Study Group [14,15]. The group consisted of medical doctors who volunteered to dedicate their daily standard clinical work to scientific analysis. The study was performed in primary care settings. Patients with type 2 diabetes aged between 20 and 70 years who visited each clinic/hospital from January 2004 to December 2005 and whose diabetes was diagnosed before 2003 were included in this study. The participants were not different from background patients ($n = 16\ 394$) of the JDDM study in terms of clinical characteristics described in a previous report [14], where a large-scale study of the daily management of diabetes at multiple clinics and hospitals in Japan was first demonstrated. Patients with type 1 diabetes were excluded. Treatment goals recommended by the Japan Diabetes Society (JDS) were glycosylated haemoglobin A1C (A1C) <6.5%, blood pressure (BP) <130/80 mmHg and serum concentrations of total cholesterol (TC) <5.17 mmol/L (200 mg/dL), triglycerides (TG) <1.68 mmol/L (150 mg/dL) and HDL cholesterol (HDL) >1.03 mmol/L (40 mg/dL) [16]. The JDDM study group has an independent ethical committee comprising a lawyer, a sociologist, a patient with type 2 diabetes and a medical doctor not majoring in diabetes. The study protocol was approved by the ethical committees of the JDDM and each clinic. Data collection from the software was performed after subtracting patients' ID and name and replacing them with a coded clinic-ID, and the database for the study was originated by an independent company. All patients gave written informed consent and the study was carried out in accordance with Helsinki Declaration II.

Measurements

Type 2 diabetes was diagnosed according to the JDS criteria, i.e. fasting blood glucose ≥6.99 mmol/L (126 mg/dL) or casual blood glucose ≥11.10 mmol/L (200 mg/dL), and mostly not treated with insulin in the first year after diagnosis [16]. Overweight was defined as BMI ≥25.0 kg/m^2. The presence of cardiovascular diseases (CVD) was diagnosed by the physician as a history of ischaemic stroke, coronary heart disease (CHD) and/or peripheral arterial disease (PAD). Stroke (ischaemic cerebrovascular disease) included only symptomatic brain infarction, and did not include silent brain infarction, transient ischaemic attack or brain haemorrhage. CHD included a previous history of myocardial infarction, angina pectoris, the presence of coronary interventions or the presence of ECG abnormalities suggestive of CHD, which was confirmed by a physician. PAD was diagnosed by an ankle-brachial pressure index of <0.9 and/or two absent foot pulses. Diabetic retinopathy was assessed by fundus photography after pupillary dilation and graded as none, simple or proliferative retinopathy. Smoking was defined as never/past/current. Neuropathy was diagnosed in patients with two or more of the following three components: presence of symptoms, absence of ankle tendon reflexes or abnormal scores of vibration perception threshold using a C128 tuning fork, where bilateral spontaneous pain, hypoesthesia or paraesthesias of the legs were considered as the neuropathic symptoms.

BP was measured with an appropriate-sized cuff in the sitting position after 5-min rest, and the average of three measurements on different days was recorded. The pulse pressure (PP) was defined as the difference between systolic and diastolic BP. Hypertension was defined by a systolic blood pressure (SBP) of >140 mmHg or a diastolic blood pressure (DBP) of >90 mmHg, or both, or patients already being treated with antihypertensive drugs. Non-fasting blood samples were obtained for measurements of A1C and serum concentrations of lipids. Each laboratory measured A1C by high-performance liquid chromatography. The normal range of A1C was from 4.3 to 5.8%. The method was standardized by the JDS and was calibrated using a control agent. Hyperlipidaemia was defined by serum concentrations of TC of >5.69 mmol/L or TG >1.68 mmol/L or HDL <1.03 mmol/L or patients already being treated by lipid lowering agents.

Serum and urinary concentrations of creatinine were measured by an enzymatic method. The inter-laboratory coefficient of variation for the creatinine value was <5%. Urinary albumin was measured in random urine samples using a turbidimetric immunoassay with the lowest

detection limit of 0.5 μg/mL. The urinary albumin excretion rate (AER) was presented as the albumin-to-creatinine ratio (ACR; mg/g creatinine). The measurement of ACR was performed at 12 laboratories using the same method. Laboratory-to-laboratory variation was evaluated by measuring the same urine samples, and the coefficient of variation was 10.5% at a mean ACR of 28.6 mg/g creatinine, 22.9% at 47.0 mg/g creatinine and 10.9% at 306.5 mg/g creatinine as previously reported [15].

The eGFR was calculated using the following equation, originated from the MDRD study group [9,10], and refitted for Japanese individuals as just recently recommended by the Japanese Society of Nephrology : eGFR (mL/min/1.73 m^2) = 194 × $Scr^{-1.094}$ × $Age^{-0.287}$ × 0.739 (if female) [17]. At first, patients were stratified by eGFR values (mL/min/1.73 m^2) into five CKD stages as per the National Kidney Foundation guidelines [13]: CKD 1, eGFR ≥90; CKD 2, eGFR 60–89; CKD 3, eGFR 30–59; CKD 4, eGFR 15–29; and CKD 5, <15 mL/min/1.73 m^2. Then we combined CKD stages 1 and 2 into a single category, since eGFR could be underestimated when the value is >60 as compared to the measured GFR [12]. Renal insufficiency, i.e. low eGFR, was defined as an eGFR <60. Nephropathy was staged as follows: normoalbuminuria, ACR <30; microalbuminuria, ACR ≥30 and <300; macroalbuminuria, ACR ≥ 300, in at least two of three consecutive samples.

Statistical analysis

Results are given as mean ± SD unless otherwise stated. Statistical significance of the differences between the groups was determined by chi-squared tests for categorical variables and unpaired Student's *t*-test for continuous variables. Comparison of clinical variables among the groups was performed by one-way analysis of variance. Multiple logistic regression was used to describe the associations of variables with the presence of renal insufficiency and micro/macroalbuminuria controlling for potential confounders. The validity of the model was confirmed by conducting the likelihood-ratio test (Hosmer–Lemeshow test). The *P*-values under 5% (two-tailed) were considered to be significant. All analyses were performed with the statistical software package SPSS (Dr SPSS II version, SPSS Japan Inc., Tokyo, Japan).

Results

Clinical characteristics of patients according the stages of nephropathy and CKD

The clinical and metabolic parameters of patients are shown according to the nephropathy stages (Table 1) and CKD stages (Table 2). The parameters that commonly aggravated albuminuria stages and CKD stages were age, duration of

Table 1. Clinical characteristics of diabetic patients according to the nephropathy stages ($N = 3297$)

	Nephropathy stages			*P*-value
	Normoalbuminuria $N = 2298$	Microalbuminuria $N = 705$	Macroalbuminuria $N = 294$	
Age (years)	58 ± 8	59 ± 8	60 ± 8	0.0025
Male (%)	63.2	65.8	66.7	0.2860
BMI (kg/m^2)	24.4 ± 3.5	25.4 ± 3.8	26.1 ± 4.8	<0.0001
BMI ≥25 (%)	38.0	49.5	52.4	<0.0001
Duration of diabetes (years)	10 ± 8	12 ± 8	14 ± 8	<0.0001
Diet/tablet/insulin (%)	16/66/18	9/68/23	4/56/40	<0.0001
A1C (%)	7.0 ± 1.0	7.3 ± 1.2	7.4 ± 1.3	<0.0001
Serum creatinine (μmol/L)	65.4 ± 15.0	66.3 ± 18.6	122.9 ± 145.9	<0.0001
Hypertension (%)	42.0	58.1	77.8	<0.0001
SBP (mmHg)	127 ± 14	132 ± 14	135 ± 15	<0.0001
DBP (mmHg)	74 ± 9	76 ± 9	77 ± 9	<0.0001
PP (mmHg)	53 ± 11	56 ± 12	58 ± 13	<0.0001
Hyperlipidaemia (%)	60.8	63.4	75.3	<0.0001
TC (mmol/L)	5.12 ± 0.80	5.22 ± 0.91	5.28 ± 1.09	0.0006
HDL (mmol/L)	1.42 ± 0.41	1.42 ± 0.49	1.34 ± 0.41	0.0019
TG (mmol/L)[a]	1.32 (0.92–1.94)	1.42 (0.97–1.99)	1.69 (1.15–2.40)	<0.0001
Smoking current/past/never (%)	30/21/49	35/19/47	36/24/40	0.0070
CVD (%)	7.1	12.9	18.0	<0.0001
Retinopathy proliferative/simple/ no (%)	5/18/77	15/27/58	28/45/27	<0.0001
Neuropathy (%)	18.8	25.5	49.0	<0.0001
Attainment rate (%)				
A1C <6.5%	32.0	23.2	23.8	<0.0001
BP <130/80 mmHg	46.8	36.1	21.8	<0.0001
Lipids	34.4	32.4	24.4	0.0030
TC <5.17 and TG <1.68 and HDL≥1.03 mmol/L				

[a]Median and interquartile ranges are given.

BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

Table 2. Clinical characteristics of diabetic patients according to the CKD stages ($N = 3297$)

	CKD stages				*P*-value
	eGFR ≥60	eGFR 30–59	eGFR 15–29	eGFR <15	
	CKD 1–2 $N = 2791$	CKD 3 $N = 459$	CKD 4 $N = 31$	CKD 5 $N = 16$	
Age (years)	58 ± 8	63 ± 6	61 ± 5	58 ± 6	<0.0001
Male (%)	65.1	58.4	64.5	50.0	0.0280
BMI (kg/m^2)	24.7 ± 3.7	25.0 ± 3.9	26.1 ± 4.2	24.6 ± 4.0	0.0564
BMI ≥25 (%)	41.5	42.7	58.1	25.0	0.1400
Duration of diabetes (years)	11 ± 7	13 ± 8	18 ± 10	17 ± 7	<0.0001
Diet/tablet/insulin (%)	14/67/19	12/59/29	3/52/45	0/31/69	<0.0001
A1C (%)	7.1 ± 1.1	6.9 ± 1.0	6.7 ± 1.0	7.1 ± 1.4	0.0153
Serum creatinine (μmol/L)	62.1 ± 12.5	93.1 ± 18.9	204.2 ± 51.3	632.9 ± 282.0	<0.0001
Hypertension (%)	45.1	65.7	96.8	87.5	<0.0001
SBP (mmHg)	128 ± 14	131 ± 15	142 ± 19	141 ± 24	<0.0001
DBP (mmHg)	75 ± 9	75 ± 10	78 ± 11	80 ± 13	0.0484
PP (mmHg)	53 ± 11	56 ± 13	65 ± 13	62 ± 14	<0.0001
Hyperlipidaemia (%)	60.7	72.1	90.0	75.0	<0.0001
TC (mmol/L)	5.15 ± 0.85	5.17 ± 0.85	5.28 ± 1.19	5.09 ± 0.98	0.6055
HDL (mmol/L)	1.42 ± 0.44	1.37 ± 0.41	1.22 ± 0.39	1.22 ± 0.41	0.0003
TG (mmol/L)[a]	1.34 (0.92–1.94)	1.52 (1.12–2.20)	1.83 (1.18–2.42)	1.71 (1.25–2.62)	<0.0001
Smoking current/past/ never (%)	32/21/47	25/21/54	32/29/39	31/13/56	0.0490
CVD (%)	7.6	17.9	32.3	12.5	<0.0001
Retinopathy proliferative/simple/no (%)	8/21/71	12/31/57	55/32/13	62/38/0	<0.0001
Neuropathy (%)	20.8	31.2	58.1	81.3	<0.0001
Attainment rate (%)					
A1C <6.5%	28.9	30.3	48.4	43.8	0.0590
BP <130/80 mmHg	43.6	37.7	6.5	12.5	<0.0001
Lipids	34.0	29.2	13.3	18.8	0.0120
TC <5.17 and TG <1.68 and HDL≥1.03 mmol/L					

[a]Median and interquartile ranges are given.
BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

Table 3. Number (proportion and its 95% CI) of patients with type 2 diabetes classified by CKD stages and albuminuria stages in the JDDM study ($N = 3297$)

	Normoalbuminuria $N = 2298$ (69.7, 68.1–71.3)	Microalbuminuria $N = 705$ (21.4, 20.0–22.8)	Macroalbuminuria $N = 294$ (8.9, 7.9–9.9)
CKD 1–2 $N = 2791$ (84.7, 83.4–85.9)	$N = 2036$ (61.8, 60.1–63.4)	$N = 600$ (18.2, 16.9–19.5)	$N = 155$ (4.7, 4.0–5.4)
CKD 3 $N = 459$ (13.9, 12.7–15.1)	$N = 259$ (7.9, 6.9–8.8)	$N = 105$ (3.2, 2.6–3.8)	$N = 95$ (2.9, 2.3–3.5)
CKD 4 $N = 31$ (0.9, 0.6–1.3)	$N = 3$ (0.1, 0.0–0.2)	$N = 0$	$N = 28$ (0.8, 0.5–1.2)
CKD 5 $N = 16$ (0.5, 0.2–0.7)	$N = 0$	$N = 0$	$N = 16$ (0.5, 0.2–0.7)

CKD, chronic kidney disease.

diabetes, levels of systemic BP and PP, serum concentrations of HDL and TG, use of insulin and proportion of hypertension, hyperlipidaemia, retinopathy, neuropathy and CVD. Proportions of men and smokers and A1C increased according to albuminuria stage, but decreased according to CKD stage. The attainment rate for treatment goals of A1C, BP and lipids decreased according to albuminuria stages and CKD stages, except that the attainment rate of A1C <6.5% did not change according to CKD stages.

Proportion of patients stratified by the stages of CKD and nephropathy

Cross-classification by CKD stages and albuminuria stages and the proportion of patients (95% CI) are demonstrated in Table 3. The proportion of subjects with an eGFR <60 was 15.3% (506/3297; 95% CI: 14.1–16.6%) in the study sample, while it was 11.4% (262/2298; 95% CI: 10.1–12.7%) among those with normoalbuminuria, 14.9% (105/705; 95% CI: 12.3–17.5%) among those with microalbuminuria and 47.3% (139/294; 95% CI: 41.6–53.0%) among those with macroalbuminuria.

Associated clinical factors for albuminuria and low eGFR (Table 4)

Clinical factors that were associated with both albuminuria (normo/micro/macroalbuminuria) and low eGFR (≥60/<60) were duration of diabetes, PP, hypertension, CVD, retinopathy and neuropathy. Age, low A1C and non-smoking were only associated with low eGFR. A1C, SBP, DBP, TG and smoking were only associated with albuminuria.

Table 4. Clinical profiles in patients by status of albuminuria and renal insufficiency

		Normoalbuminuria eGFR <60; $N = 262$ eGFR ≥60; $N = 2036$	Microalbuminuria eGFR <60; $N = 105$ eGFR ≥60; $N = 600$	Macroalbuminuria eGFR <60; $N = 139$ eGFR ≥60; $N = 155$	*P*-value among groups with normo/micro/ macroalbuminuria
Age (years)	eGFR <60	62 ± 6****	64 ± 5****	61 ± 6****	0.0090
	eGFR ≥60	57 ± 9	58 ± 8	58 ± 8	0.4209
Male (%)	eGFR <60	52.7***	64.8	64.7	0.0220
	eGFR ≥60	64.6	66.0	68.4	0.5530
BMI (kg/m^2)	eGFR <60	24.8 ± 3.7	25.0 ± 3.8	25.6 ± 4.4*	0.1910
	eGFR ≥60	24.3 ± 3.5	25.4 ± 3.8	26.7 ± 5.0	<0.0001
BMI ≥25 (%)	eGFR <60	40.5	43.8	47.5	0.3950
	eGFR ≥60	37.7	50.5	56.2	<0.0001
Duration of diabetes (years)	eGFR <60	11 ± 8***	14 ± 9**	17 ± 9****	<0.0001
	eGFR ≥60	10 ± 7	12 ± 7	12 ± 8	<0.0001
A1C (%)	eGFR <60	6.8 ± 0.9	7.0 ± 0.9*	7.1 ± 1.2****	0.0077
	eGFR ≥60	7.0 ± 1.0	7.3 ± 1.2	7.7 ± 1.3	<0.0001
SBP (mmHg)	eGFR <60	130 ± 16*****	133 ± 15	137 ± 16	<0.0001
	eGFR ≥60	127 ± 14	131 ± 14	134 ± 15	<0.0001
DBP (mmHg)	eGFR <60	75 ± 10	74 ± 10**	77 ± 10	0.0284
	eGFR ≥60	74 ± 9	76 ± 9	77 ± 9	<0.0001
PP (mmHg)	eGFR <60	55 ± 13***	59 ± 14***	60 ± 13	0.0002
	eGFR ≥60	53 ± 11	55 ± 11	56 ± 12	<0.0001
Hypertension (%)	eGFR <60	58.2****	69.5*	86.3**	<0.0001
	eGFR ≥60	39.9	56.1	69.7	<0.0001
Hyperlipidaemia (%)	eGFR <60	71.6****	68.9	79.7	0.1180
	eGFR ≥60	59.4	62.4	71.2	0.0090
TC (mmol/L)	eGFR <60	5.19 ± 0.78**	5.12 ± 0.85	5.42 ± 1.37	0.7562
	eGFR ≥60	5.09 ± 0.83	5.22 ± 0.93	5.33 ± 1.09	<0.0001
HDL (mmol/L)	eGFR <60	1.37 ± 0.36	1.40 ± 0.51	1.27 ± 0.41**	0.0119
	eGFR ≥60	1.42 ± 0.41	1.42 ± 0.49	1.40 ± 0.39	0.5120
TG (mmol/L)[a]	eGFR <60	1.46 (1.12–2.18)****	1.48 (1.09–2.04)	1.76 (1.18–2.36)	0.0242
	eGFR ≥60	1.30 (0.90–1.89)	1.41 (0.96–1.98)	1.62 (1.10–2.53)	<0.0001
Smoking current/past/ never (%)	eGFR<60	23/18/59**	23/23/54*	34/25/41	0.0100
	eGFR ≥60	30/22/48	37/18/45	37/24/39	0.0150
CVD (%)	eGFR <60	12.6***	22.9**	26.6***	0.0010
	eGFR ≥60	6.4	11.2	10.3	<0.0001
Retinopathy proliferative/ simple/no (%)	eGFR <60	4/19/77	18/35/47 d)	37/50/12****	<0.0001
	eGFR ≥60	5/18/77	14/26/60	19/40/41	<0.0001
Neuropathy (%)	eGFR <60	20.0	38.5**	58.7**	<0.0001
	eGFR ≥60	18.6	23.3	40.1	<0.0001

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$,****$P < 0.0001$ versus patients with an eGFR ≥60.
[a] Median and interquartile ranges are given.
BMI: body mass index, A1C: glycosylated haemoglobin A1C, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, TC: total cholesterol, HDL: HDL-cholesterol, TG: triglycerides, CVD: cardiovascular disease.

Factors associated with the presence of renal insufficiency and albuminuria were explored by multiple logistic regression analysis (Table 5). Age, sex, BMI, duration of diabetes, A1C, hypertension, hyperlipidaemia, smoking, CVD, retinopathy, neuropathy and renal insufficiency (or albuminuria) were entered as independent variables in the model after adjustment for an effect of different clinics/hospitals. Factors commonly associated with renal insufficiency and albuminuria were hypertension, CVD and proliferative retinopathy. Factors independently associated with renal insufficiency were age, duration of diabetes, A1C (negative), hyperlipidaemia, smoking (negative) and macroalbuminuria, whereas factors independently associated with albuminuria were male sex, BMI, A1C, simple retinopathy, neuropathy and eGFR <60.

Clinical profile of patients with normoalbuminuria and low eGFR (Table 4)

Among the 262 patients with normoalbuminuria and with low eGFR, 198 (75.6%, 95% CI: 70.4–80.8%) had no diabetic retinopathy, and 166 (63.4%, 95% CI: 57.5–69.2%) had no diabetic neuropathy in addition. As compared with those with normoalbuminuria and preserved eGFR, those with normoalbuminuria and low eGFR were older and more often women, had higher prevalences of hypertension, hyperlipidaemia and CVD, had higher levels of SBP, PP, TC and TG and included fewer smokers. As compared with those with micro/macroalbuminuria and low eGFR, normoalbuminuric patients with low eGFR were characterized by a significantly higher proportion of women, lower prevalences of hypertension, smoking,

Table 5. Determinants of low eGFR (<60 versus ≥60; left panel) and albuminuria (micro/macroalbuminuria versus normoalbuminuria; right panel) by multiple logistic regression analysis

	eGFR<60 versus ≥60 (reference)			Micro/macroalbuminuria versus normoalbuminuria (reference)		
	Wald χ^2 score	OR (95% CI)	*P*-value	Wald χ^2 score	OR (95% CI)	*P*-value
Age (per years)	76.3	1.08 (1.06–1.10)	0.000	1.9	1.01 (1.00–1.02)	0.170
Male	0.8	0.89 (0.68–1.17)	0.386	8.3	1.31 (1.09–1.57)	0.004
BMI (per kg/m^2)	3.1	1.03 (0.99–1.06)	0.078	22.6	1.06 (1.03–1.08)	0.000
Duration of diabetes (per years)	4.4	1.02 (1.00–1.03)	0.037	0.45	1.00 (0.99–1.02)	0.504
A1C (per %)	15.3	0.79 (0.70–0.89)	0.000	29.8	1.26 (1.16–1.36)	0.000
Hypertension	10.0	1.46 (1.16–1.86)	0.002	68.7	2.12 (1.77–2.53)	0.000
Hyperlipidaemia	9.7	1.47 (1.15–1.86)	0.002	0.9	1.09 (0.91–1.31)	0.338
Smoking versus never	5.1	0.77 (0.62–0.97)	0.030	2.0	1.16 (0.95–1.42)	0.158
CVD	15.7	1.87 (1.37–2.55)	0.000	14.5	1.69 (1.29–2.29)	0.000
Retinopathy versus none						
simple	7.4	1.47 (1.11–1.91)	0.151	52.1	2.10 (1.72–2.56)	0.000
proliferative	15.9	2.11 (1.46–3.05)	0.000	80.0	3.72 (2.79–4.96)	0.000
Neuropathy (%)	1.9	1.17 (0.92–1.56)	0.174	12.3	1.45 (1.18–1.79)	0.000
Nephropathy versus normoalbuminuria				N.A.	N.A.	N.A.
Microalbuminuria	0.4	1.01 (0.83–1.45)	0.506			
Macroalbuminuria	102.1	5.56 (4.00–7.76)	0.000			
eGFR <60 versus ≥60	N.A.	N.A.	N.A.	31.1	1.91 (1.52–2.40)	0.000

Both analyses were obtained after adjustment for an effect of different clinics/hospitals.
N.A., not applicable.

CVD, retinopathy and neuropathy, and lower values of diabetes duration, systemic BP and PP. The prevalence of normoalbuminuria among those with low eGFR was 262/506 (51.8%, 95% CI: 47.4–56.1%). It was then calculated after excluding 80 of 262 patients whose normoalbuminuric status was possibly altered by the use of the renin–angiotensin system (RAS) inhibitor. After this adjustment the prevalence of normoalbuminuria among those with low eGFR was 182 of 426 (42.7%, 95% CI: 38.0–47.4%).

Discussion

This study, in a large-scale population of Japanese type 2 diabetes, indicated that the proportion of subjects with low eGFR was 11.4% among those with normoalbuminuria, 14.9% among those with microalbuminuria and 47.3% among those with macroalbuminuria. The prevalence of normoalbuminuria among patients with low eGFR was as high as 42.7% even after adjustment for the RAS inhibitor effect. This finding supports the concept that patients with type 2 diabetes can commonly progress to a significant degree of renal insufficiency while remaining normoalbuminuric [3,9]. Furthermore, we found that more than 60% of patients with normoalbuminuria and low eGFR had neither diabetic retinopathy nor neuropathy. The finding strongly suggests that non-diabetic renal disease is not uncommon in type 2 diabetic patients [2].

Clinical features of patients with normoalbuminuria and renal insufficiency

Few reports have analysed the clinical characteristics of type 2 diabetic patients with normoalbuminuria and renal insufficiency. One report compared them with those with micro/macroalbuminuria and with renal insufficiency [3]. It showed that normoalbuminuric renal insufficiency patients were characterized by female predominance, lower SBP and higher HDL, which is in accordance with our findings. Similar findings were demonstrated in type 1 diabetes [5]. We have extended their findings by demonstrating lower prevalences of smokers, CVD, retinopathy and neuropathy. Another report compared them with those with normoalbuminuria and an eGFR ≥60, where the finding was similar to ours in terms of more women, older age and higher concentrations of TC and TG [4]. Our study provides further information such as higher levels of systemic BP and PP in those with renal insufficiency and with normoalbuminuria.

Proportion of patients with normoalbuminuria and with renal insufficiency

First, we should acknowledge that the proportion of patients with renal insufficiency is subject to the equation for eGFR. The proportion of 11.4% (low eGFR among those with normoalbuminuria) shown in this paper was 16.6% when the equation in the previous studies [12,15] was employed (data not shown). Secondly, one should be cautious about selection bias when calculating prevalences. The proportion of normoalbuminuria seems higher than in other cross-sectional large-scale-population-based prevalence studies [15,18], and it is possible that the included subjects had a lower prevalence of complications compared to the entire population of type 2 diabetic patients since inpatients and those who were treated solely by cardiologists/neurologists did not participate. The prevalence of renal insufficiency among those with normoalbuminuria was 12.7% (84/660) in a report from Brazil [4], which seems compatible with our finding of 11.4%. The prevalence of normoalbuminuria

among those with renal insufficiency was 23.2% (20/86) in a report from Australia [3], but 42.7% (182/426) in our study: both studies performed adjustment for possible effects of the RAS inhibitor. The prevalence of 23.2% [3] was calculated at a tertiary referral clinic and the number was small. The above findings suggest that a significant proportion of type 2 diabetic patients have non-albuminuric renal insufficiency.

Factors associated for albuminuria and low eGFR

The clinical factors associated with albuminuria and low eGFR were comparable with those found in other longitudinal [5,9] and cross-sectional [3,4,6,19] studies. The UK Prospective Diabetes Study revealed that over a median of 15 years' follow-up, risk factors for development of albuminuria were male sex, TG, LDL-C, A1C, smoking and retinopathy, and those for renal insufficiency were female sex, age and neuropathy [9]. A female predilection for normoalbuminuria and renal insufficiency has been noted by other cross-sectional [3,4,6] and follow-up [5] studies, but to date the reason for this association is unknown. Lower A1C values were observed in those with low eGFR than in those with preserved eGFR in our study, particularly in those with micro/macroalbuminuria. This could be due to a reduced erythropoietin production caused by reduced renal function [20], although our study did not collect data for haemoglobin concentrations. A decreased haemoglobin concentration has been shown to be an independent factor associated with renal dysfunction in diabetic patients [21]. Smoking is associated with albuminuria, suggesting that smoking may be an important correlate of albuminuria in the presence or absence of low eGFR. Subjects who had never smoked were more prevalent in those with low eGFR than in those with preserved eGFR among those with normo- and microalbuminuria. The same result was seen in another report [19]; however, the reason remains uncertain from these cross-sectional studies. Taken together, distinct factors associated with albuminuria and low eGFR are indicated. Indeed, no significant associations between renal insufficiency and microalbuminuria were found in multivariate analysis. These findings support the concept that albuminuria and low eGFR are not necessarily linked in type 2 diabetes [9].

Reason for low eGFR in type 2 diabetic patients

The mechanism for low eGFR in normoalbuminuric type 2 diabetic patients is still unknown, despite the involvement of non-diabetic renal disease being indicated. Among normoalbuminuric patients, greater age, longer duration of diabetes and higher prevalences of hypertension, hyperlipidaemia, diabetic neuropathy and CVD were found in those with low eGFR than in those with preserved eGFR. A lower concentration of HDL was observed in macroalbuminuric patients with renal insufficiency. These findings indicate that low eGFR could be due to age-associated senescence and interstitial fibrosis, and renal ischaemia due to intrarenal arteriosclerosis and cholesterol emboli involvements [2,22]. Lipid abnormalities by high TG and low HDL were indicated in association with progression of renal dysfunction [23]. Our finding that the prevalence of CVD was persistently twofold higher in patients with low eGFR than in those with preserved eGFR regardless of the degree of albuminuria indicates that the low eGFR is substantially associated with atherosclerotic vascular disease.

Limitation of the study

The study design was cross-sectional; therefore it cannot explore causal relationships. A single measurement of serum creatinine for calculating eGFR could mislead the classification of CKD stages. Since age and female sex both reduce the MDRD equation, it cannot be denied that the association of these factors with low eGFR was generated in part by the equation. Direct measurement of GFR should be a standard clinical procedure, although it is time consuming and not feasible for screening and large-scale studies. The usefulness of eGFR has been demonstrated by several follow-up studies [24,25], and a recent validation study indicated that the difference between eGFR by MDRD and measured GFR was slight and not significant even in cross-sectional analysis of normoalbuminuric and albuminuric diabetic patients [5]. On the other hand, the strengths of this study include the large-scale population with type 2 diabetes, a nation-wide multicentre-based design and multiple measurements of ACR and blood pressure. Finally, since the subjects included in this study were recruited from practice and seemed less complicated, we cannot evaluate the prevalence of severe renal failure from this study although it is likely to be higher than we have found.

Attainment of treatment goals

The low attainment rate of treatment goals for A1C, BP and lipids may indicate that those with increasing albuminuria stages and CKD stages are refractory to standard therapy despite aggressive use of insulin, antihypertensive and lipid-lowering agents. This finding is in line with other studies [26], indicating the need for aggressive treatment of these modifiable risk factors. In diabetic patients even without albuminuria, it may be reasonable to encourage screening for low eGFR. The potential benefit of achieving current treatment goals in patients with micro/macroalbuminuria and/or low eGFR offers hope for the future reduction of CVD and end-stage renal disease if a more focused and multifactorial approach is applied.

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