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ORIGINAL ARTICLE

Japan Diabetic Nephropathy Cohort Study: study design, methods, and implementation

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Abstract
Background Diabetic nephropathy, leading to end-stage renal disease, has a considerable impact on public health and the social economy. However, there are few national registries of diabetic nephropathy in Japan. The aims of this prospective cohort study are to obtain clinical data and urine samples for revising the clinical staging of diabetic nephropathy, and developing new diagnostic markers for early diabetic nephropathy.
Methods The Japanese Society of Nephrology established a nationwide, web-based, and prospective registry system. On the system, there are two basic registries; the Japan Renal Biopsy Registry (JRBR), and the Japan Kidney Disease Registry (JKDR). In addition to the two basic registries, we established a new prospective registry to the system; the Japan Diabetic Nephropathy Cohort Study (JDNCS), which collected physical and laboratory data.
Results We analyzed the data of 321 participants (106 female, 215 male; average age 65 years) in the JDNCS. Systolic and diastolic blood pressure was 130.1 and 72.3 mmHg, respectively. Median estimated glomerular filtration rate (eGFR) was 33.3 ml/min/1.73 m^2. Proteinuria was 1.8 g/gCr, and serum levels of albumin were 3.6 g/dl. The majority of the JDNCS patients presented with preserved eGFR and low albuminuria or low eGFR and advanced proteinuria. In the JRBR and JKDR registries, 484

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and 125 participants, respectively, were enrolled as having diabetes mellitus. In comparison with the JRBR and JKDR registries, the JDNCS was characterized by diabetic patients presenting with low proteinuria with moderately preserved eGFR.

Conclusions There are few national registries of diabetic nephropathy to evaluate prognosis in Japan. Future analysis of the JDNCS will provide clinical insights into the epidemiology and renal and cardiovascular outcomes of type 2 diabetic patients in Japan.

Keywords Diabetic nephropathy · Cohort study · Estimated glomerular filtration rate · Japan Diabetic Nephropathy Cohort Study · Japan Renal Biopsy Registry · Japan Kidney Disease Registry

Introduction

The most serious issue in clinical nephrology is the relentless and progressive increase in patients with end-stage renal disease in Japan [1, 2]. Today, diabetic nephropathy has a considerable impact on society in the fields of public health and social economy; many physician scientists are involved in research to elucidate the pathogenesis of diabetic nephropathy and the prevention and cure of the disease.

However, there are few national registries of diabetic nephropathy in Japan. The Committee for the Working Group for Renal Biopsy Database in the Japanese Society of Nephrology established a nationwide, web-based, and prospective registry system, with or without renal biopsy—the Japan Renal Biopsy Registry (JRBR) and the Japan Kidney Disease Registry (JKDR) respectively, from 2007 [3]. However, these two registries have no follow-up data. Therefore, we have established a nationwide prospective diabetic nephropathy cohort—the Japan Diabetic Nephropathy Cohort Study (JDNCS). The aims of this prospective cohort study are to obtain clinical data and urine samples for revising the clinical staging of diabetic nephropathy, and developing new diagnostic markers for early diabetic nephropathy. The JDNCS is now prospectively collecting clinical data annually.

The aim of the current study was to compare baseline characteristics of JDNCS patients with the diabetic patients on the JRBR and the JKDR. Long-term follow-up of the JDNCS patients will provide clinical insights into the epidemiology and renal and cardiovascular outcomes of diabetic nephropathy.

Subjects and methods

Registry system

The researchers on the Committee for the Diabetic Nephropathy Research, which was supported by the Ministry of Health, Labour and Welfare of Japan, participated in this study. The report includes data from patients on the JRBR and JKDR, registered prospectively from January 2007. Patient data including age, gender, laboratory data, and clinical and pathological diagnoses were electronically recorded at each institution and registered on the web page of the JRBR and JKDR utilizing the system of Internet Data and Information Center for Medical Research (INDICE) in the University Hospital Medical Information Network (UMIN). JDNCS patient data were also electronically recorded at each institution and registered on the web page of the INDICE system in UMIN. The ethical committee of the Kanazawa University and the Japanese Society of Nephrology

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comprehensively approved the study, and a local committee of participating centers and their affiliated hospitals individually approved the study. Written informed consent was obtained from the patients at the time of biopsy or before participation in the study. The JRBR is registered to the Clinical Trial Registry of UMIN (registered number UMIN000000618) and is available in Japanese and English.

Screening and enrollment

Entry criteria to the JDNCS were adult type 2 diabetic patients with early to advanced nephropathy. Exclusion criteria to the JDNCS were patients <20 years at entry, patients with type 1 diabetes, secondary diabetes, and/or overt primary kidney diseases. Baseline information and laboratory data of eligible patients were collected.

Clinical information and laboratory data

Diagnosis of diabetes mellitus (DM) was performed by the attending physician, and recorded on the database. Whole blood and serum were collected for measurement of hemoglobin, creatinine, protein, albumin, plasma glucose, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol. HbA1c measured by the Japanese Diabetes Society (JDS) method was corrected to the A1C value measured by the National Glycohemoglobin Standardization Program (NGSP) method by adding 0.4 % as determined by the JDS. Estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR (ml/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $Age^{-0.287}$ (for men) and eGFR (ml/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $Age^{-0.287}$ × 0.739 (for women) [4]. Spot urine samples were collected for measurement of albuminuria, proteinuria, and urine creatinine. In the JDNCS, data of both albuminuria and proteinuria were collected, but only data of proteinuria were collected in the JRBR and JKDR. Urine samples were collected and stocked in cases with agreement for future biomarker analysis.

Statistics

Statistical analyses were performed using the SPSS Statistics software program, version 19 (SPSS Inc., NY, USA). Comparisons of categorical variables among groups of different indications or diagnoses were performed using Fisher's exact test. Kolmogoov–Smirnov test was used to evaluate normal or non-normal distribution. Continuous variables were compared using the Student's t test for parametric data and Wilcoxon's signed rank test or the Kruskal–Wallis test for non-parametric data. P values of <0.05 (obtained by two-tailed testing) were considered to indicate statistical significant difference. Normal distribution data were expressed by mean ± SD, and non-normal distribution data were expressed by median and interquartile range (IQR).

Results

Characteristics of entry data to the JDNCS

Data for the JDNCS were collected from 321 patients (106 female, 215 male) with a median age of 65 years (IQR 59.0–74.0). Systolic and diastolic blood pressure, HbA1c (NGSP) levels, eGFR, proteinuria, serum levels of albumin, and serum levels of total cholesterol in JDNCS patients were 130.1 ± 17.3, 72.3 ± 11.6 mmHg, 6.8 (IQR 5.8–7.1) %, 33.3 (IQR 17.1–58.2) ml/min/1.73 m^2, 1.8 (IQR 0.3–4.9) g/gCr, 3.6 (IQR 3.2–4.1) g/dl, and 181.0 (IQR 52.0–208.8) mg/dl, respectively. 36.8 % of patients were treated by insulin, 11.8 % used angiotensin-converting enzyme inhibitors, 61.4 % used angiotensin receptor blockers, and 41.1 % used statins.

Distribution of eGFR and albuminuria in the JDNCS

When categorized by degree of eGFR and albuminuria, the majority of patients presented with preserved eGFR and low albuminuria, or low eGFR and advanced proteinuria (Table 1). The proportion of patients with an eGFR ≥60 ml/min/1.73 m^2 and albuminuria <30 mg/gCr was approximately 30 %, and the proportion with an eGFR <30 ml/min/1.73 m^2 and albuminuria ≥300 mg/gCr was approximately 20 % in the JDNCS. However, the proportion of patients with low eGFR (<30 ml/min/1.73 m^2) and low albuminuria (<30 mg/gCr), or preserved eGFR (≥60 ml/min/1.73 m^2) and advanced albuminuria (≥300 mg/gCr) was approximately 1 and 6 %, respectively.

Characteristics of JDNCS entry data in GFR stages

JDNCS entry data for eGFR is shown in Table 2. Duration of DM was prolonged in proportion to advanced GFR stage. Systolic blood pressure increased in association with decreasing eGFR, but diastolic blood pressure was not significantly different. Serum levels of total protein and albumin decreased in proportion to advanced GFR stage. There was no statistically significant difference among GFR stages in LDL and HDL cholesterol, and triglycerides. Although there is no statistically significant difference, albuminuria tended to increase in proportion to advanced

Table 1 Distribution of eGFR and albuminuria in JDNCS patients at entry

JDNCS ($N = 259$)	Albuminuria (mg/gCr)						Total (%)
		<10	10–29	30–299	300–1999	≥2000	
GFR (ml/min/1.73 m^2)	≥90	1.9	3.9	2.7	0.4	0.8	9.7
	60–89	13.9	11.2	7.7	3.5	1.5	37.8
	45–59	2.3	4.2	5.0	4.2	2.7	18.4
	30–44	1.2	1.5	0.8	2.7	5.4	11.6
	15–29	0.4	0.0	0.8	3.1	7.3	11.6
	<15	0.8	0.0	0.0	3.5	6.6	10.9
Total (%)		20.5	20.8	17.0	17.4	24.3	100.0

GFR stage. Hb and HbA1c decreased in proportion to advanced GFR stage.

Characteristics of JDNCS entry data in albuminuria stages

In addition to GFR stages, JDNCS entry data was shown in terms of albuminuria stages (Table 3). Systolic blood pressure increased in proportion to advanced albuminuria stage, but diastolic blood pressure was not significantly different. Serum levels of total protein and albumin decreased in proportion to advanced albuminuria stage. Triglycerides increased in proportion to advanced albuminuria stage, but total cholesterol (Tcho), LDL and HDL cholesterol was not significantly different. eGFR was significantly decreased in Stage A3.

Comparison of JDNCS patients with diabetic patients in JRBR and JKDR

The JRBR and JKDR contained 484 patients (143 female, 341 male) and 125 patients (31 female, 94 male), respectively (Table 4; Fig. 1). HbA1c levels (JDS) were similar among the three groups [JDNCS 6.3 (IQR 5.8–7.1) %, JRBR 6.2 (IQR 5.5–7.0) %, JKDR 6.1 (IQR 5.7–6.9) %]. The patients in the JDNCS (65.0; IQR 59.0–74.0 years) were older than kidney biopsy-proven diabetic patients in the JRBR (61.0; IQR 53.0–66.0 years). Moreover, the JDNCS patients showed lower levels of proteinuria and serum levels of total cholesterol, and higher serum levels of albumin [1.8 (IQR 0.3–4.9) g/gCr, 181.0 (IQR 152.0–208.8) mg/dl, 3.6 (IQR 3.2–4.1) g/dl, respectively] than the JRBR patients [4.0 (IQR 1.4–8.1) g/gCr, 210.0 (IQR 173.8–255.3) mg/dl, 3.1 (IQR 2.3–3.8) g/dl, respectively]. eGFR was higher in JDNCS patients [33.3 (IQR 17.1–58.2) ml/min/1.73 m^2] than JKDR patients [13.6 (IQR 5.3–31.5) ml/min/1.73 m^2]. Systolic and diastolic blood pressure was lower in JDNCS patients (130.1 ± 17.3, 72.3 ± 11.6 mmHg, respectively) than JRBR patients (145.9 ± 21.5, 79.6 ± 14.1 mmHg, respectively).

Discussion

The JDNCS aimed to evaluate the epidemiology and long-term renal and cardiovascular outcomes of diabetic nephropathy. The JDNCS enrolled 321 Japanese diabetic patients with early to advanced nephropathy. Median eGFR was 33.3 (IQR 17.1–58.2) ml/min/1.73 m^2, and proteinuria was 1.8 (IQR 0.3–4.9) g/gCr at entry. The majority of JDNCS patients presented with preserved eGFR and low albuminuria, or low eGFR and advanced proteinuria. In comparison with JDNCS patients, JRBR diabetic patients showed lower serum albumin levels with advanced proteinuria, while JKDR diabetic patients showed lower eGFR with advanced proteinuria.

The JDNCS study enrolled Japanese diabetic patients with preserved to low eGFR and normoalbuminuria to massive proteinuria. eGFR and proteinuria are clinically important prognostic factors for adverse outcomes, including renal and cardiovascular events, and death [5]. Moreover, macroalbuminuira was the main predictor of mortality, independently of both eGFR and cardiovascular risk factors [6, 7]. However, in patients with normoalbuminuria, eGFR provided no further information for all-cause mortality and cardiovascular mortality [6]. There has been a nationwide and yearly statistical survey of chronic dialysis patients since 1968, conducted by the Japanese Society for Dialysis Therapy in Japan [8]. The combined data of the three registries with this dialysis registry will allow us to evaluate the long-term outcome of patients with diabetic nephropathy in the near future. Moreover, JDNCS is prospectively collecting clinical data annually. Therefore, the JDNCS will provide prognostic data of diabetic patients in Japan.

Although the majority of JDNCS patients presented with preserved eGFR and low albuminuria, or low eGFR and advanced proteinuria at entry, approximately 10 % of JDNCS patients showed an eGFR <60 ml/min/1.73 m^2 and albuminuria <30 mg/gCr. Yokoyama et al. [9] also reported that the proportion of subjects with low eGFR (<60 ml/min/1.73 m^2) and normoalbuminuria was 11.4 % of type 2

Table 2 Characteristic of JDNCS entry data for GFR stage

eGFR stage	Stage G1		Stage G2		Stage G3A		Stage G3B		Stage G4		Stage G5		*P* value
	Mean/ median	SD/IQR	Mean/ median	SD/IQR	Mean/ median	SD/IQR	Mean/ median	SD/IQR	Mean/ median	SD/IQR	Mean/ median	SD/IQR	
Age	57.5	10.5	66.2	9.0	67.3	11.6	68.4	11.4	67.2	9.7	68.1	10.3	0.000
Duration	9.5	8.7	13.2	9.2	16.3	10.3	14.5	9.1	15.4	11.9	19.1	10.0	0.001
HT	163.1	8.7	160.0	8.9	159.1	9.8	159.9	9.3	162.2	8.6	159.9	8.5	0.409
BW	68.9	18.7	64.8	13.8	65.0	14.9	66.2	12.9	62.8	11.1	63.8	19.6	0.492
BMI	26.0	5.7	25.0	4.3	25.8	4.4	25.9	4.5	23.9	3.7	25.0	7.4	0.109
SBP	127.2	16.9	126.8	15.5	128.9	16.4	127.1	15.6	137.6	21.1	144.2	14.9	0.000
DBP	72.3	8.8	73.6	10.3	70.4	11.8	71.1	12.2	74.1	14.9	71.2	13.9	0.514
sCr	0.56	0.10	0.76	0.12	1.01	0.20	1.45	0.25	2.35	0.46	4.73	1.67	0.000
sTPro	7.2	0.6	7.1	0.6	7.0	0.8	6.7	0.9	6.6	1.0	6.4	0.8	0.000
Alb	4.1	0.5	4.1	0.5	3.8	0.7	3.7	0.7	3.3	0.6	3.4	0.6	0.000
PG	166.1	74.0	154.5	59.1	156.5	51.1	139.3	56.7	133.4	46.3	129.6	61.8	0.003
Tcho	170.1	42.5	189.9	39.6	174.5	43.8	174.4	44.4	204.2	54.5	187.5	64.4	0.034
LDL	96.0	24.4	101.4	31.6	98.0	28.2	88.6	36.1	115.1	43.5	95.8	45.2	0.149
HDL	51.2	19.0	51.9	18.9	46.4	12.5	48.2	15.6	50.5	18.9	51.8	28.0	0.784
TG	97.5	62.0–151.3	116.5	84.3–172.3	108.0	73.0–143.0	84.0	61.0–161.5	125.0	101.0–232.5	141.5	87.8–215.5	0.212
HbA1c	7.7	6.0–9.3	6.7	6.3–7.9	6.7	5.9–7.4	6.3	6.0–7.4	5.8	5.0–8.0	7.1	6.2–7.4	0.003
Hb	13.5	2.2	13.7	1.5	13.0	1.7	11.9	2.0	11.0	1.6	9.7	1.8	0.000
ACR	22.9	6.9–107.0	21.3	9.7–68.8	90.6	20.8–205.9	17.7	5.5–219.4	250.0	37.0–1354.6	166.5	1.1–504.8	0.083
eGFR	103.6	12.0	72.4	8.4	52.4	4.6	36.2	4.4	22.5	4.0	10.7	2.8	0.000

Kruskal–Wallis test was used for analysis. TG, HbA1c, and ACR were expressed by median and interquartile range (IQR), and the others were expressed by mean and SD

Duration duration of DM, *HT* height, *BW* body weight, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, hemoglobin, *sCr* serum levels of creatinine, *sTPro* serum levels of total protein, *Alb* albumin, *PG* plasma glucose, *Tcho* total cholesterol, *LDL* LDL cholesterol, HDL cholesterol, *TG* triglyceride, *ACR* urinary albumin-creatinine ratio

Table 3 Characteristics of JDNCS entry data in albuminuria stages

Albuminuria stages	Stage A1		Stage A2		Stage A3		*P* value
	Mean/median	SD/IQR	Mean/median	SD/IQR	Mean/median	SD/IQR	
Age	64.4	10.1	68.2	9.8	64.8	11.1	0.131
Duration	13.2	9.8	15.2	9.4	15.4	10.6	0.222
HT	159.8	9.6	160.7	8.6	161.5	9.0	0.430
BW	65.5	14.6	63.2	13.1	65.2	15.9	0.584
BMI	25.0	23.2–27.6	25.5	21.4–28.0	24.4	23.8–31.0	0.129
SBP	126.1	15.7	131.1	17.8	135.7	18.6	0.000
DBP	71.9	11.5	72.7	10.2	72.7	12.4	0.803
sCr	0.84	0.69–1.01	0.86	0.69–1.11	1.08	0.75–1.93	0.000
sTPro	7.1	0.4	7.3	0.6	6.5	1.0	0.000
Alb	4.1	3.8–4.4	4.2	3.8–4.4	4.0	3.5–4.27	0.000
PG	134.0	110.3–168.5	172.0	114.0–218.0	162.5	146.8–199.3	0.022
Tcho	180.0	159.8–204.3	187.0	157.0–203.0	171.0	143.3–199.3	0.948
LDL	96.0	78.8–105.0	96.0	77.0–115.0	102.5	76.5–122.8	0.544
HDL	50.9	16.5	47.4	12.6	51.3	22.0	0.469
TG	93.0	72.8–152.3	125.0	103.0-173.0	120.0	87.5–164.8	0.045
HbA1c	6.5	6.0–7.3	7.1	6.4–8.4	6.8	5.9–7.4	0.001
Hb	13.4	1.6	13.6	1.9	11.5	2.2	0.000
ACR	10.6	5.5–17.9	72.8	44.4–124.2	618.5	376.9–1104.7	0.000
eGFR	69.4	20.6	70.4	25.7	35.4	23.7	0.000

Kruskal–Wallis test was used for analysis. BMI, sCr, Alb, PG, Tcho, LDL, TG, HbA1c, and ACR were expressed by median and interquartile range (IQR), and the others were expressed by mean and SD

Duration duration of DM, *HT* height, *BW* body weight, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, hemoglobin, *sCr* serum levels of creatinine, *sTPro* serum levels of total protein, *Alb* albumin, *PG* plasma glucose, *Tcho* total cholesterol, *LDL* LDL cholesterol, HDL cholesterol, *TG* triglyceride, *ACR* urinary albumin–creatinine ratio

Table 4 Comparison of JDNCS with JRBR and JKDR

	JDNCS			JRBR			JKDR				
	n	Mean/median	SD/IQR	*n*	Mean/median	SD/IQR	*n*	Mean/median	SD/IQR	JDNCS vs. JRBR	JDNCS vs. JKDR
Gender	321	F 106	M 215	484	F 143	M 341	125	F 31	M 94		
Age	321	65.0	59.0–74.0	484	61.0	53.0–66.0	125	66.0	60.0–73.0	<0.001	0.548
BW	321	65.0	14.8	452	65.6	14.3	125	63.0	121.1	0.589	0.168
BMI	300	23.9	21.8–27.3	484	24.4	21.2–27.2	125	23.3	21.4–25.9	<0.001	0.021
SBP	312	130.1	17.3	327	145.9	21.5	122	142.1	24.2	<0.001	<0.001
DBP	321	72.4	11.6	326	79.6	14.1	122	73.0	13.7	<0.001	0.605
HbA1c	321	6.3	5.8–7.1	322	6.2	5.5–7.0	117	6.1	5.7–6.9	0.329	0.007
eGFR	312	33.3	17.1–58.2	484	43.6	30.5–61.5	125	13.6	5.3–31.5	<0.001	<0.001
Alb	318	3.6	3.2–4.1	475	3.1	2.3–3.8	125	3.6	3.0–4.0	<0.001	0.001
Tcho	266	181.0	152.0–208.8	456	210.0	173.8–255.3	125	180.5	154.8–221.0	<0.001	0.012
U–p/cr	148	1.8	0.3–4.9	253	4.0	1.4–8.1	92	3.4	1.2–6.5	<0.001	0.006

BW body weight, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Alb* albumin, *Tcho* total cholesterol, *U-P/Cr* urinary protein-creatinine ratio

diabetic patients examined. These clinical characteristics were more common among female patients, particularly if retinopathy and/or hypertension were also present [10]. Although patients with advanced proteinuria and low eGFR are major and high risk for end-stage kidney disease, patients with normoalbuminuria and low eGFR show a

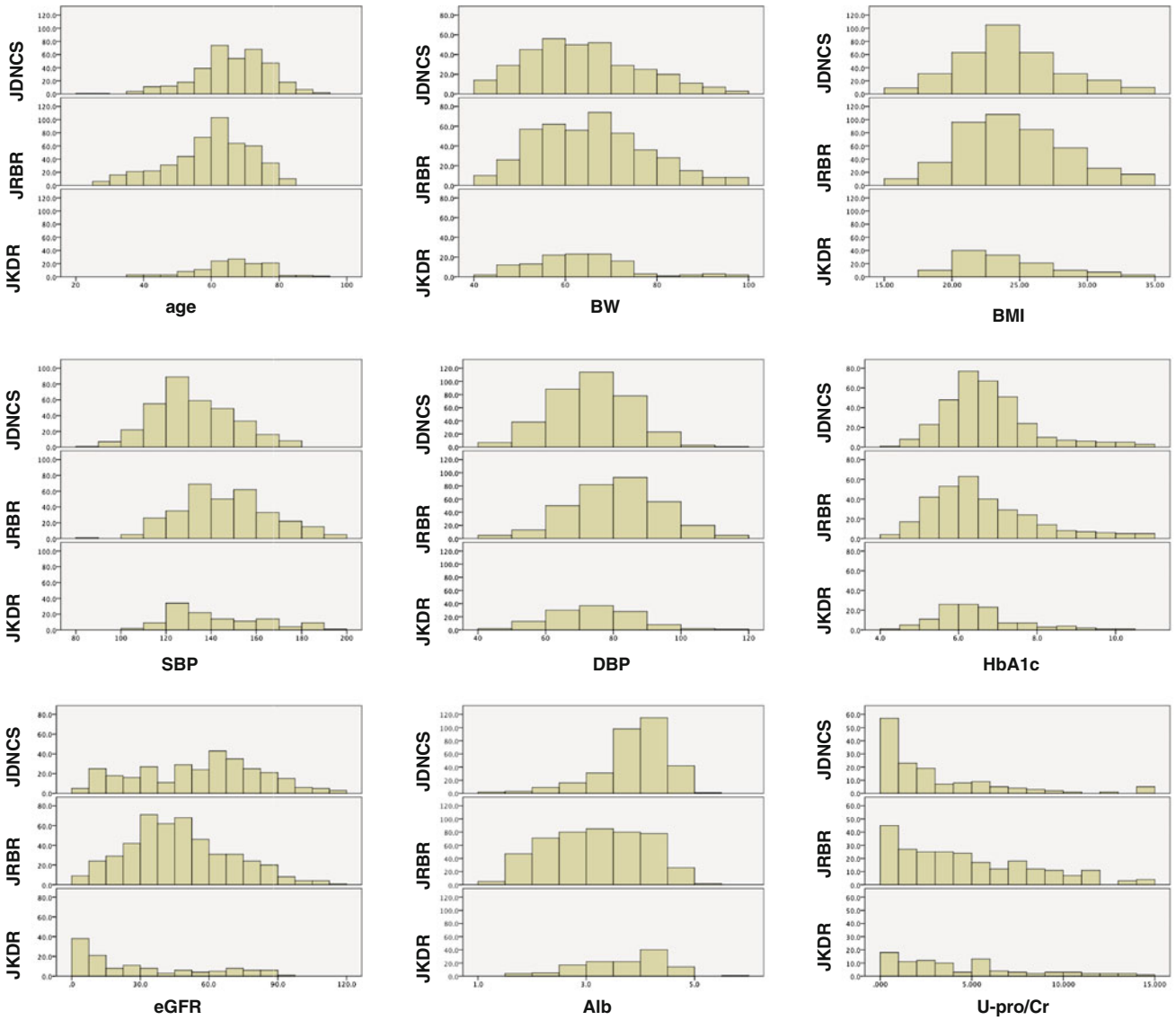

Fig. 1 Distribution of age, body weight (BW), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, estimated glomerular filtration ratio (eGFR), serum levels of albumin, and urinary levels of protein and creatinine ratio (U-pro/Cr) in JDNCS, JRBR, and JKDR

unique characteristic kidney outcome. Moreover, pathological manifestations of these normoalbuminuria and low eGFR patients were so far unclear. Pathological characteristics and grading would be required to understand the pathophysiology of diabetic nephropathy in more depth together with future perspectives. Kidney biopsy samples are essential to evaluate the relationship between histological findings and clinical manifestation or kidney outcome; however, kidney biopsy is rarely performed in diabetic nephropathy patients. Therefore, the 484 kidney biopsy samples of the JRBR are certainly valuable. Accordingly, clinical long-term follow-up data from the JDNCS together with the JRBR biopsy samples will be useful for evaluating clinical and pathological characteristics of this typical subgroup in future.

In this study, we compared data from two registries and one cohort study. The main objectives of the registry were to establish the frequency of kidney disease based on the histopathological findings (JRBR), or clinical diagnosis (JKDR). In addition to the frequency of diabetic kidney disease in kidney biopsy or clinical diagnosis, this study revealed that entry data of the diabetic patients in these three registries were characteristically different. The basic data from these three registries will be important for evaluating the results from each registry relatively. Although, overt primary kidney diseases were excluded

from these registries and cohort, it is difficult to clearly distinguish between diabetic nephropathy and primary kidney disease in a general clinical setting. This is a limitation of these studies. Moreover, the JRBR and JKDR had no follow-up data. In contrast to these two cross-sectional registries, the JDNCS is a prospective cohort study to evaluate cardiovascular events and progression of kidney dysfunction. Future analysis of data from these two registries and one cohort will provide valuable clinical and pathological information of type 2 diabetes in Japan.

In conclusion, there are few national registries of diabetic nephropathy to evaluate prognosis in Japan. Future analysis of prospective cohort studies, such as the JDNCS, will provide clinical information on epidemiology, and renal and cardiovascular outcomes of type 2 diabetic patients in Japan.

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Conflict of interest The authors have declared that no conflict of interest exists.

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