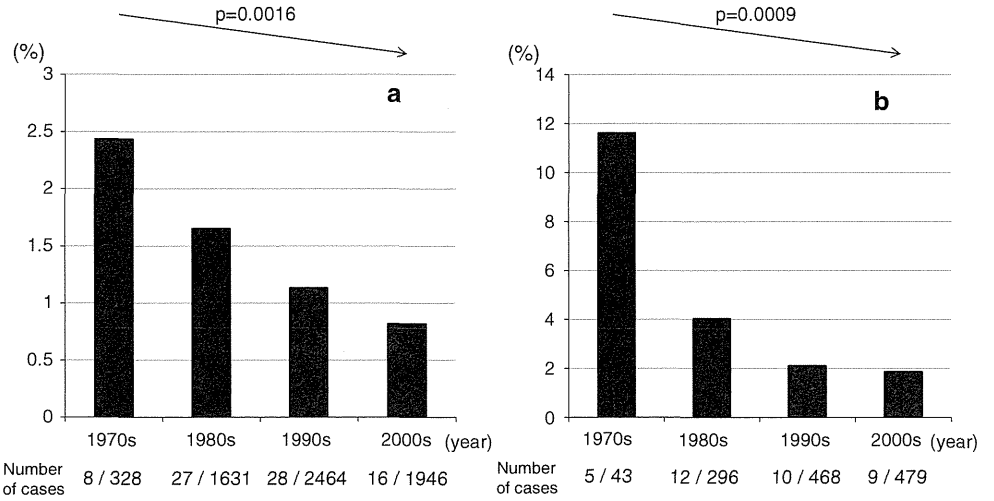

Fig. 1 Distribution of primary MPGN in total biopsies (**a**) and in biopsies with nephrotic syndrome (**b**) over four decades. Both trend tests were statistically significant

the renal biopsy], but the trends in both periods were not statistically significant ($p = 0.2384$).

Discussion

Long-term studies of the rate of primary GN involving over four decades of data are limited throughout the world as well as in Japan. In the present report, we demonstrated that the rate of primary MPGN showed a downward trend over time. Moreover, we statistically revealed a decline in pediatric cases; in particular, the disappearance of pediatric cases with nephrotic syndrome in the 1990s and 2000s was characteristic. By contrast, although the rate of primary MPGN in adults was one-third or one-fourth of that in children, the decrease in adult patients with primary MPGN was not established in the present study.

Some examinations of the change in the rate of MPGN in industrialized countries have been previously reported (Table 1). Major reports from Italy and Spain dealing with patients of all age groups showed that the rate of MPGN statistically decreased from the 1970s to the 1980s [3, 5]. Meanwhile, Swaminathan et al. [6] reported that the rate of MPGN in the USA remained statistically unchanged according to a comparison among the 1970s, 1980s, and 1990s; however, this result and conclusion may have been limited because of the small sample size. The following discussion focuses on an age-based analysis. The decrease of adult patients in industrialized countries is unclear. Jungers et al. [7] reported on a comparative examination of French patients >15 years; the rate of MPGN in France statistically decreased between the 1970s and 1980s. Chang et al. [8] reported on a comparative examination of Korean patients >15 years; the rate of MPGN in Korea statistically decreased between the 1980s and 2000s. By contrast, Braden et al. [9] reported a change in the rate of MPGN in adults with >2 g of daily urinary protein. The rate of MPGN in the USA remained statistically unchanged

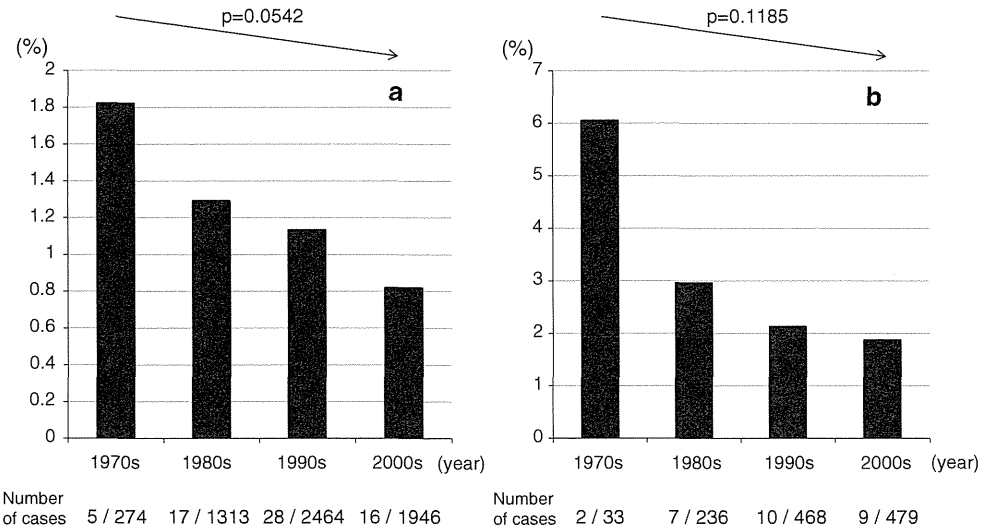

Fig. 2 Distribution of primary MPGN in adult patients (**a**) and patients with nephrotic syndrome (**b**) over four decades. The differences between the groups were not statistically significant

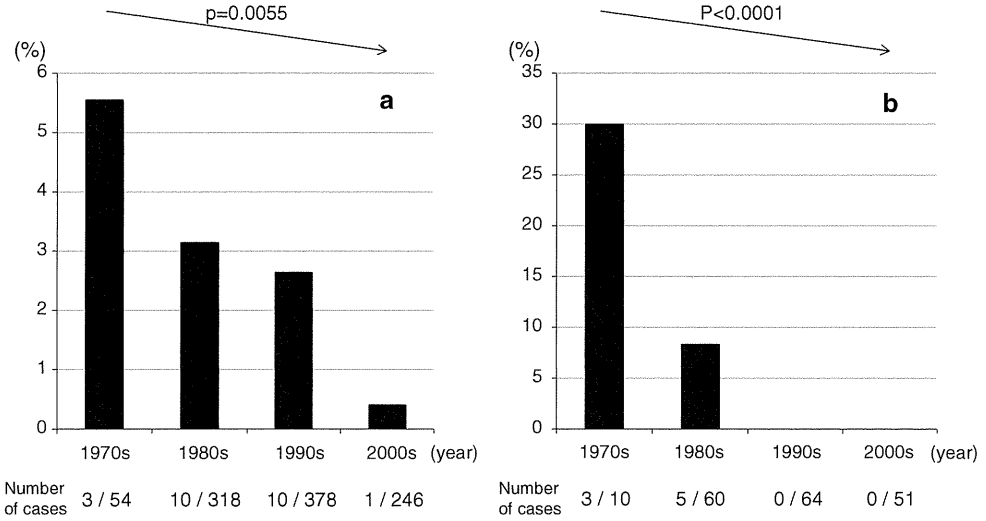

Fig. 3 Distribution of primary MPGN in child patients (**a**) and patients with nephrotic syndrome (**b**) over four decades. Both trend tests were statistically significant

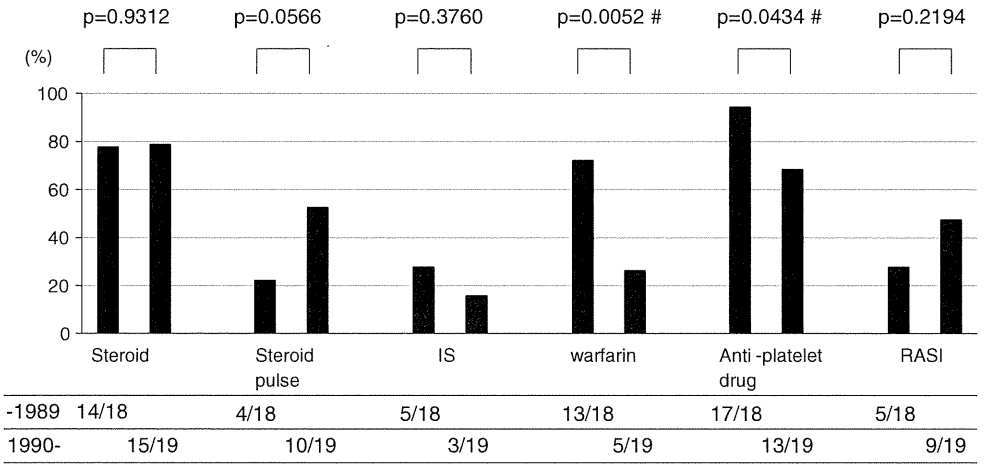

Fig. 4 The secular change in the treatment of primary MPGN. Use of steroid pulse therapy was higher in the more recent group (1990s and 2000s). By contrast, the administration of warfarin and anti-platelet drugs was statistically decreased in the more recent group (*hash symbols*). *IS* immunosuppressive drug, *RASI* renin–angiotensin system inhibitor

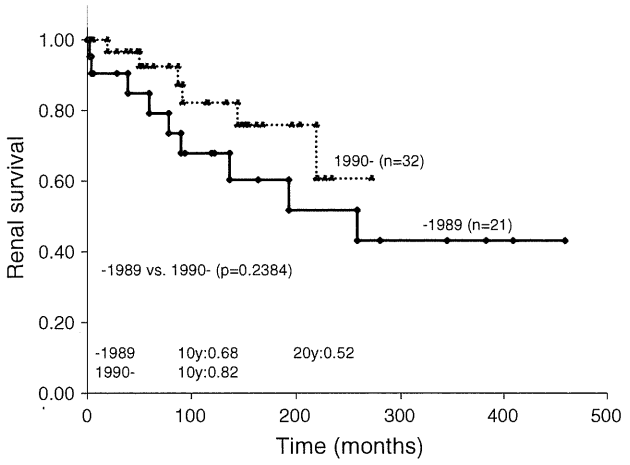

Fig. 5 The secular change in clinical outcomes of primary MPGN. Renal survival was analyzed by Kaplan–Meier method. The difference in renal survival between both periods was not statistically significant

according to a comparison among the 1970s, 1980s, and 1990s. Thus, the decline in adult patients with MPGN in industrialized countries remains statistically unconfirmed. On the other hand, the decrease in child patients with MPGN in industrialized countries (Spain and Japan) was statistically significant [10, 11]. The Study Group of the Spanish Society of Nephrology reported a comparative examination of Spanish patients <15 years of age in the 1970s and 1980s [10]. Iitaka et al. [11] reported on a comparative examination of Japanese patients <15 years of age in the 1970s, 1980s, and 1990s. Moreover, West reported on a comparative examination of child patients in the USA [12]. The rate of MPGN onset was seen to be on a declining trend from the 1970s to the 1980s without statistical analysis. Important differences in the above-mentioned results include the difference in the samples, differences in the race of the individuals sampled or the surrounding environment, the rarity of the disease, and the

possibility of including secondary MPGN. Additionally, the data for the 1990s and 2000s remain insufficient compared with the data for the 1970s and 1980s.

By contrast, the decrease in MPGN in developing countries has never been confirmed. In the Middle East (Saudi Arabia), South America (Peru), and Africa (Nigeria), MPGN remains one of the most common causes of nephrotic syndrome and may account for 30–40 % of all cases [1]. Moreover, the decrease of child patients with primary MPGN in Turkey and of adult patients with primary MPGN in Brazil were not statistically significant (Table 1) [13, 14]. The epidemiological pattern of glomerular diseases in developing countries is distinct from that in industrialized countries [15]. MPGN is the most common primary GN in developing countries, whereas IgA nephropathy is uncommon. The reason for the difference in the epidemiological patterns may be a key to elucidating the mechanism of MPGN onset. Some external factors associated with the hygienic environment and socioeconomic problems, e.g., infection control (especially the control of chronic bacterial, viral, and parasitic infections), have been discussed [1, 2, 15]. Japan is currently one of the most developed countries in the world. After World War II, Japan achieved outstanding economic growth; there was a period of high economic growth from 1956–1973, and a period of stable economic growth from 1974–1990 (reference web page in Japanese: Cabinet Office, Government of Japan. http://www.cao.go.jp/). Therefore, the socio-economic status of Japan developed very quickly in the 1970s and maintained slow progress after the 1970s. The average income in a particular area can be used as an index of the area's socio-economic status. According to the government data for 2009, the average income in Ibaraki Prefecture (2,653,000 yen per resident) was almost the same as the national average (2,791,000 yen per resident) (reference web page: Cabinet Office, Government of Japan.). Therefore, the present results for Ibaraki Prefecture reflect those for Japan as a whole. Additionally, the nation's sanitation and public health developed rapidly after World War II. A number of Schools of Hygiene and Public Health were concurrently established on the basis of a proposal made by the government of the United States. Moreover, laws related to hygiene and public health were established, e.g., the School Health Act was established in 1956 and the Water Supply Act in 1957. Therefore, disease control, immunization, school health, environmental pollution control, the deployment of water supply and sewage systems, and food sanitation progressively improved. All of these developments led to decreases in a variety of infections. Previous reports from Japan mentioned that some infections such as tuberculosis (since the 1980s), hepatitis A virus (since the 1990s), and parasites (*Schistosomiasis japonica*, since the 1980s) were decreasing [16–18]. Johnson et al. [15] suggested that the overall hygiene and socioeconomic status of a country may predispose its citizens to either a Th1- or Th2-dominant phenotype that will increase the susceptibility of that population to specific types of glomerular disease. The Th1-dominant glomerular diseases, such as MPGN and non-IgA mesangial proliferative GN, are more common in impoverished countries. By contrast, the Th2-dominant glomerular diseases, such as IgA nephropathy and minimal change nephrotic syndrome, are common in industrialized countries. It is generally thought that early and frequent exposure to bacterial and other antigens, common in developing countries, leads to a normal Th1 response. However, better public hygiene and fewer infections may lead to the persistence of the Th2 response and thereby increase the risk for developing allergies. In Japan, the incidence of atopic disorder also increased from the 1970s to the 1990s [19]. Moreover, Holdsworth et al. [20] reported that most proliferative GNs were driven by the Th1 response. Thus, the hygiene hypothesis may explain the epidemiologic change in glomerular diseases including primary MPGN. Our result regarding the reduction of child cases in Japan, an industrialized country, may help explain the mechanism of the decrease in primary MPGN. For example, some key changes have occurred in sanitary conditions and in the epidemiology of infectious diseases in children in Japan. In the future, worldwide research about epidemiologies is needed.

In the present study, we statistically proved a reduction in the incidence of primary MPGN. It is necessary to elucidate the reasons for the decrease in primary MPGN. Explaining this decrease may lead to a breakthrough in understanding the onset mechanism of primary MPGN.

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Conflict of interest We declare that we have no conflicts of interest.

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ORIGINAL ARTICLE

Membranous nephropathy in Japan: analysis of the Japan Renal Biopsy Registry (J-RBR)

Hitoshi Yokoyama · Takashi Taguchi · Hitoshi Sugiyama · Hiroshi Sato · On behalf of the Committee for the Standardization of Renal Pathological Diagnosis and for Renal Biopsy and Disease Registry in the Japanese Society of Nephrology

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Abstract Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. The J-RBR/J-KDR registry developed by the Japanese Society of Nephrology provides nationwide cohort data for epidemiological studies of MN. MN was present in 36.8% of 1,203 primary nephrotic syndrome patients in Japan. In addition, 633 (77.9%) out of 813 MN patients were referred to as "idiopathic," whereas 22.1% were classified as "secondary" and involved conditions such as systemic lupus erythematosus, drug exposure, infections, cancer, and various collagen diseases. The mean age of the MN patients was 62.2 (2–88) years old, their mean eGFR was 76.7 (7.6–154.6) ml/min/1.73 m^2, and 63.3% had hypertension at the time of renal biopsy. On the basis of these findings, half of Japanese idiopathic MN patients have risk factors (age >60, male, or lower eGFR) for end-stage renal failure, and 10% belong to the high-risk group (daily proteinuria of over 8.0 g). Further studies with high-grade evidence should resolve the natural history and therapeutic problems of idiopathic MN in elderly Japanese.

Keywords Membranous nephropathy · Epidemiology · Nephrotic syndrome

Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. Eighty percent of MN patients are referred to as "idiopathic," whereas approximately 20% of MN patients are classified as "secondary" and are associated with clinical conditions including infections, systemic lupus erythematosus (SLE), cancer, drug exposure, etc. [1–3]. It is generally felt that secondary-type cases involve exogenous antigens such as the hepatitis B virus (HBV) E antigen or tumor antigens. Idiopathic MN is considered to be an autoimmune disease because podocyte-related antigens such as neutral endopeptidase were recently identified in neonatal MN, and the M-type phospholipase A2 receptor (PLA2R) was detected in 70–80% of idiopathic MN patients [4, 5]. Although spontaneous remission of nephrotic syndrome occurs in approximately one-third of patients in Europe and North America, approximately 40% of patients develop end-stage renal failure (ESRF) after 10 years [6]. In Japan, several surveys of patients with certain renal diseases including idiopathic MN have been conducted. In a retrospective cohort study of 949 Japanese idiopathic MN patients performed between 1975 and 1993, renal survival rates judged by a requirement for hemodialysis and/or end-stage renal disease (ESRD) with serum creatinine levels ≥3.0 mg/dL

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were 90.3% of patients after 10 years and 60.5% of patients after 20 years [7].

Until recently, there were no web-based, nationwide, or prospective registry systems for renal biopsies in Japan. Thus, in 2007, the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology established the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data about the renal biopsies performed in Japan [8].

The aim of the current review was to investigate the epidemiology of MN using the data registered in the J-RBR between 2007 and 2010.

The Japan Renal Biopsy Registry (J-RBR) system, subjects, and limitations

The researchers of the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology set up the J-RBR [8]. This review includes data obtained from 8,670 patients that were prospectively registered in the J-RBR from July 2007 to September 2010. Patient data including age, gender, laboratory data, and clinical and pathological diagnoses were electronically recorded at each institution and registered on the J-RBR webpage via the Internet Data and Information Center for Medical Research (INDICE) system, which is part of the University Hospital Medical Information Network (UMIN). The ethical committee of the Japanese Society of Nephrology comprehensively approved the study, and the local committees of the participating centers and their affiliate hospitals individually approved the study. The J-RBR was registered to the Clinical Trial Registry of UMIN (UMIN000000618).

It is worth noting that a web-based prospective registry system like the J-RBR can easily increase the number of participating institutions and enlarge the number of patients enrolled. Investigators can then analyze the registered data in real time. Otherwise, we cannot exclude sampling bias and thus ensure that the present sample of patients in the J-RBR is actually representative of the nationwide frequency of renal diseases in Japan. However, an investigation of a larger cohort or a population-based analysis of the rate of each renal disease may reveal the actual frequency of the disease and the distribution of age ranges utilizing this web-based system.

Membranous nephropathy patients in the J-RBR (2007–2010) and in other countries

At the end of September 2010, 813 MN patients (9.4%) had been registered in the J-RBR. As for the frequency of MN in renal biopsied patients, previous Japanese studies reported that MN represented 10.6% of 1,850 cases of primary glomerular disease in 1999 [9] and 12.7% of 1,233 primary glomerular disease cases recorded in the J-RBR between 2007 and 2008 [8]. In other countries, MN accounted for 9.3–23.4% of primary glomerular disease cases recorded in renal biopsy registries (Table 1) [10–15]. IgA nephropathy was the most common primary glomerular disease in Japan. Thus, the frequency of MN in renal biopsied cases might be lower in Japan than in other countries because of racial differences and/or the use of different indication criteria for renal biopsy in each country. Thus, it may not be easy to compare reports across countries. However, studying the changing frequency

Table 1 The frequencies of several primary glomerular diseases in different countries in different years

	Japan [8, 9]		China [10]	Italy [11]	Czech [12]	Romania [13]	Brazil [14, 15]	
Year:	2011	1999	2004	2004	2004	2006	2006	2010
Total cases:	*n* 1223 (%)	*n* 1,850 (%)	*n* 9278 (%)	*n* 6990 (%)	*n* 2333 (%)	*n* 401 (%)	*n* 1131 (%)	*n* 4619 (%)
IgAN	54.2	47.4 (495/1045)	45.3	43.5	34.5	28.9	17.8	20.1
MN	12.7	10.6	9.9	23.4	9.3	11.2	20.7	20.7
MCD	10.5	17.5	0.9	9.2	12.5	8.5	9.1	15.5
FSGS	6.3	4.6	6.0	13.1	10.8	11.5	29.7	24.6
MPGN	2.5	7.5	3.4	6.6	4.6	29.4	7.0	4.2
Cresc GN	0.9	0.9	1.9	2.3	3.2	7.9	4.1	1.7
Non-IgAN mes PGN	10.4	–	25.6	–	11.3	–	3.8	9.9
Other unclassifiable	2.5	–	7.0	1.9	13.8	2.5	7.8	3.3
Total (%)	100	–	100	100	100	99.9	100	100

IgAN IgA nephropathy, *MN* membranous nephropathy, *MCD* minimal change disease, *FSGS* focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis, *mes PGN* mesangial proliferative glomerulonephritis

patterns of renal disease in the same country over a certain time period may be a useful way to judge alterations in disease backgrounds.

In the present analysis, 633 (77.9%) of 813 MN patients were referred to as "idiopathic," whereas 180 MN patients (22.1%) were classified as "secondary," including 74 (9.1%) lupus nephritis patients (ISN/RPS2003 classification class V), 14 patients (1.7%) whose condition had been caused by drug exposure (12 patients treated with bucillamine, a disease-modifying antirheumatic drug, DMARD), 10 patients (1.2%) with infectious disease (hepatitis B virus: 4, hepatitis C virus: 4, syphilis: 1, and human immunodeficiency virus: 1), 8 patients (1.0%) with cancer (prostatic cancer: 1, pancreatic cancer: 1) or hematological disease (post bone-marrow transplantation: 3, IgG4-related disease: 2, and monoclonal gammopathy of undetermined significance: 1), and 7 patients (0.9%) with various collagen diseases (Fig. 1a). As for the age distribution of the MN patients, around 60% of the secondary MN patients were in their second to fourth decade, and lupus nephritis (class V) was the most common primary disease among these patients. In addition, the number of registered patients increased with age and peaked in the seventh decade (Fig. 1b).

Demographics of idiopathic membranous nephropathy patients in Japan

The demographics of the 633 patients with idiopathic MN are presented in Table 2 and Fig. 2. As for gender, the male to female ratio was 1.3 (358 males and 275 females) and did not differ among the decades (Fig. 2a). In previous reports, the male to female ratio was much higher; i.e., 1.6 in 1,008 Japanese patients [7] and 2.0 in North Americans, Australians, and Asians (1,190 males and 598 females) [5, 6]. The mean age of the patients was 62.2 (2–88) years old, which was 10 years older than that in a report published in 2001 (50.7 years old) [7]. In addition, the mean eGFR of the MN patients was 76.7 (7.6–154.6) ml/min/1.73 m^2. The

Table 2 Patient demographics of idiopathic membranous nephropathy in Japan (J-RBR2007-2010)

	N	Min	Max	Mean	SD
Age (years old, y.o.)	633	2	88	62.2	14.3
Male	358	3	86	61.3	13.9
Female	275	2	88	63.5	14.6
Height (cm)	607	82	184	158.7	10.8
Weight (kg)	607	11.9	112.0	59.9	12.4
Body mass index (BMI)	607	13.7	41.1	23.6	3.7
Proteinuria (g/day)	501	0.00	26.9	3.99	3.3
Urinary protein/creatinine ratio	429	0.00	26.8	5.57	4.36
Serum creatinine (mg/dl)	632	0.17	6.6	0.88	0.49
eGFR (more than 20 y.o.)	592	7.6	154.6	76.7	26.0
Serum total protein (g/dl)	632	3.20	8.4	5.49	0.96
Serum albumin (g/dl)	627	0.70	4.99	2.64	0.83
Serum total cholesterol (mg/dl)	619	125	838	295.4	102.2
Systolic blood pressure (mmHg)	490	77	194	130.8	19.2
Diastolic blood pressure (mmHg)	490	48	156	76.9	12.5
Mean blood pressure (mmHg)	490	64	180	94.9	13. 4
HbA1c (%)	298	4.4	8.6	5.5	0.7

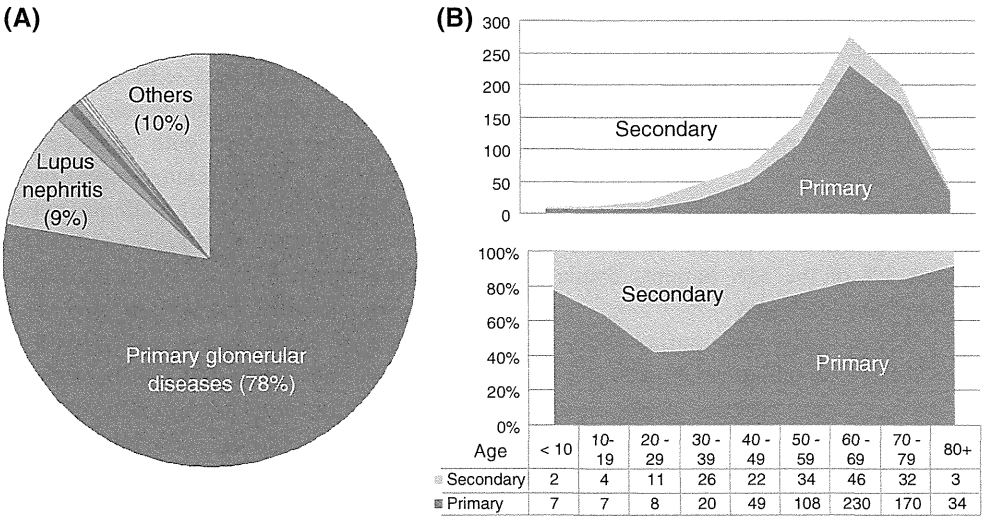

Fig. 1 Primary diseases (**a**) and ages (**b**) of membranous nephropathy patients in Japan. J-RBR 2007–2010 registry: 813 cases in total; 633 cases in which membranous nephropathy was the primary disease (77.9% of all cases)

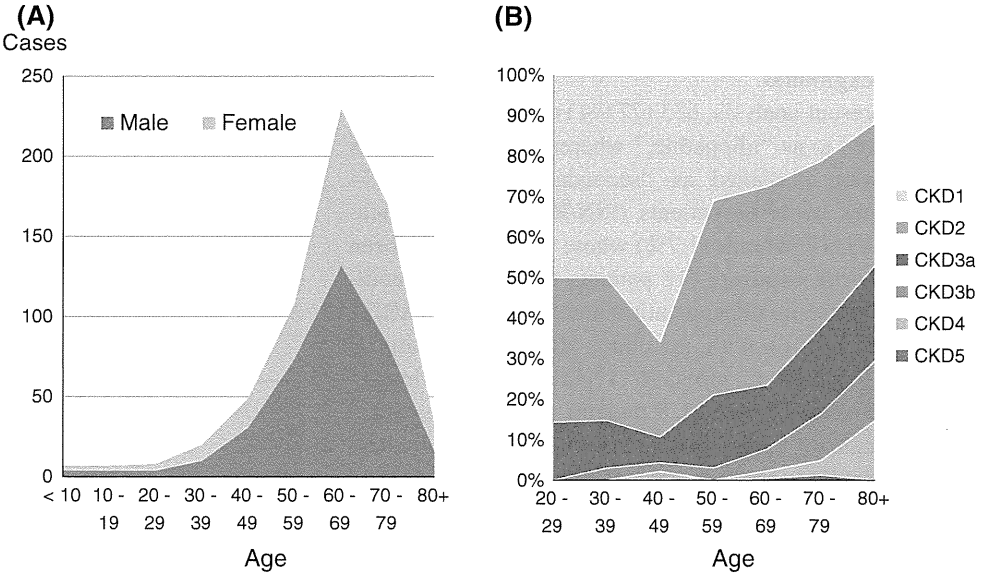

Fig. 2 Ages, genders (**a**), and CKD stages (**b**) of idiopathic membranous nephropathy patients in Japan. J-RBR 2007–2010 registry: 633 cases in total; males: 358 cases (56.6%), females: 278 cases (43.4%)

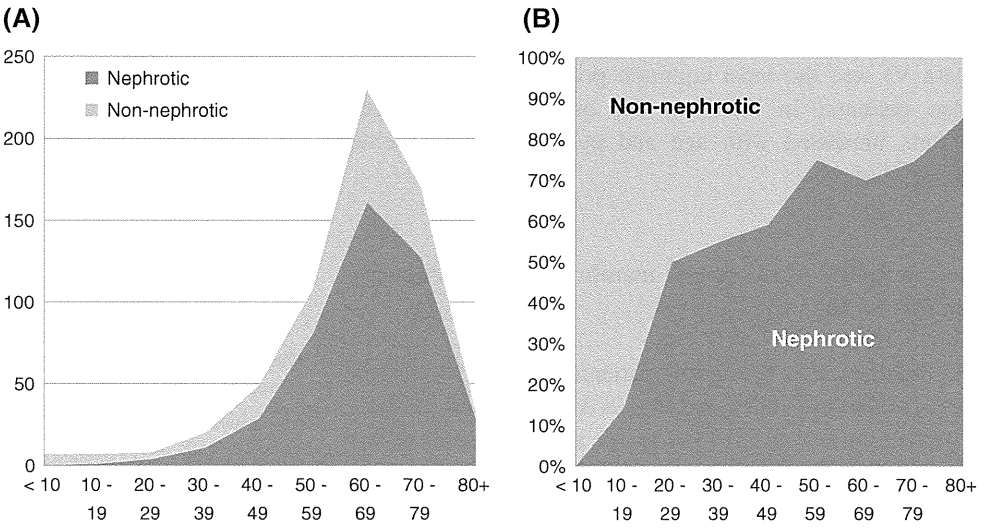

Fig. 3 Nephrotic syndrome in idiopathic membranous nephropathy and age distribution of the population. J-RBR 2007–2010 registry: nephrotic syndrome was present in 444 of 633 cases (70.0%)

number of patients with advanced chronic kidney disease (CKD) (stage 3a, 3b, or 4) [18] increased with age, and more than 20% of them were 60 years old or older. A future analysis using anti-PLA2R antibodies might explain these phenomena, such as the increased number of females and older population.

Regarding proteinuria, 70.0–91.6% of idiopathic MN patients had nephrotic syndrome in previous reports. On the other hand, about 5% of the MN patients displayed mild proteinuria of less than 1.0 g/day.

In this study, the mean daily proteinuria value was 3.99 g, and the mean urinary protein to creatinine ratio was 5.57 g/gCr. When we judged the patients' nephrotic state based on the new criteria for nephrotic syndrome used in Japan [19]; i.e., daily proteinuria (or a urinary protein to creatinine ratio if daily proteinuria was not measured) of more than 3.5 g (or g/gCr) and serum albumin levels of less than 3.0 g/dL or serum total protein levels of less than 6.0 g/dL, 444 (70%) of 633 idiopathic MN patients were considered to be nephrotic (Fig. 3a). The frequency of a nephrotic state increased with age from 0% in the first decade to 80% in the ninth decade (Fig. 3b). The high-risk group; i.e., the patients with daily proteinuria values of over 8.0 g based on a previous report on North Americans [1], included 53 (10.6%) patients out of 501 patients (12.2% of 279 males and 8.6% of 222 females, Table 3).

As for hypertension, blood pressure and/or the intake of anti-hypertensive drugs were registered in 455 idiopathic MN patients. Hypertension, as judged by a systolic blood pressure of more than 140 mmHg, a diastolic blood pressure of more than 90 mmHg, or drug intake, was observed in 308 (67.7%) patients with idiopathic MN. In addition, only 31.7% patients (153 out of 482 patients) were considered to have well-controlled blood pressure, as judged by the recommended levels outlined in the Japanese CKD guidelines [20]; i.e., a systolic blood pressure of less than

Table 3 Proteinuria of idiopathic membranous nephropathy in Japan (J-RBR2007-2010)

Proteinuria (g/day)	Total *n* 501	Percentage	Male *n* 279	Percentage	Female *n* 222	Percentage
<0.30	15	3.0	11	3.9	4	1.8
0.30–0.49	18	3.6	10	3.6	8	3.6
0.50–0.99	37	7.4	16	5.7	21	9.5
1.00–3.49	185	36.9	98	35.1	87	39.2
3.50+	246	49.1	144	51.6	102	45.9
High-risk group (≥8.0 g/day)	53	10.6	34	12.2	19	8.6

Table 4 Pathology in primary nephrotic syndrome including IgA nephropathy

	Japan		Korea [16]		Brazil [15]		USA [17]		
Year:	2011		2009		2010		1966		
Observed period:	2007–2010		1987–2006		1993–2007		1975–1994		
Biopsied cases:	8,670		1,818		9,617		1,056		
Nephrotic cases:	*n* 1,307	%	*n* 611	%	*n* 2,754	%	Total *n* 340 (%)	Black *n* 121 (%)	White *n* 170 (%)
MCNS	490	37.5	235	38.5	776	28.2	16	14	20
MN	443	*33.9*	157	*25.7*	698	*25.3*	*33*	*24*	*36*
FSGS	138	10.6	58	9.5	1013	36.8	34	57	23
IgA nephropathy	104	8.0	68	11.1	158	5.7	7	2	8
MPGN type (I/III)	66	5.0	51	8.3	71	2.6	6	2	6
Mes PGN	30	2.3	–	–	38	1.4	–	–	–
Crescentic GN	13	1.0	–	–	–	–	–	–	–
Endocapillary PGN	12	0.9	–	–	–	–	–	–	–
Sclerotic GN	2	0.2	–	–	–	–	–	–	–
Others	9	0.7	42	6.9	–	–	4	1	6
		100.0		100.0		100.0	100	100	100

Italic values are statistically significant ($p = 0.0002$)

MCNS minimal change nephrotic syndrome, *MN* membranous nephropathy, *FSGS* focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis, *Mes* mesangial, *PGN* proliferative glomerulonephritis, *GN* glomerulonephritis

125 mmHg and a diastolic blood pressure of less than 75 mmHg in patients displaying daily proteinuria of more than 1.0 g or a urinary protein to creatinine ratio of more than 1.0 g/gCr, or a systolic blood pressure of less than 130 mmHg and a diastolic blood pressure of less than 80 mmHg in patients displaying daily proteinuria of less than 1.0 g or a urinary protein to creatinine ratio of less than 1.0 g/gCr, at the time of renal biopsy. These findings revealed that Japanese patients with idiopathic MN often have insufficiently controlled hypertension at the initial presentation.

Idiopathic membranous nephropathy in nephrotic syndrome in Japan and other countries

Two thousand sixty-six patients with nephrotic syndrome were selected from the J-RBR using the previously described criteria [19]. In this population, primary glomerular disease including IgA nephropathy accounted for 63.2% of the patients, and their secondary glomerular diseases included diabetic nephropathy (9.9%), lupus nephritis (6.1%), and amyloidosis (4.2%) (Fig. 4, left). Idiopathic MN was found in 36.8% of 1,203 primary nephrotic syndrome patients without IgA nephropathy, and about 25% of all nephrotic syndrome patients (Fig. 4, right). Compared to other countries (South Korea, Brazil, and USA), the frequency of MN (33.9% of patients with nephrotic syndrome due to primary glomerular disease including IgA nephropathy) was similar to that found for Caucasians in the USA (36%), but much higher than those obtained for South Koreans (25.7%), Brazilians (25.3%), and African blacks in the USA (24%) (Table 4). These differences might reflect the age distributions of the renal biopsied patients in each area, because Japanese MN patients tend to be much older, as described below.

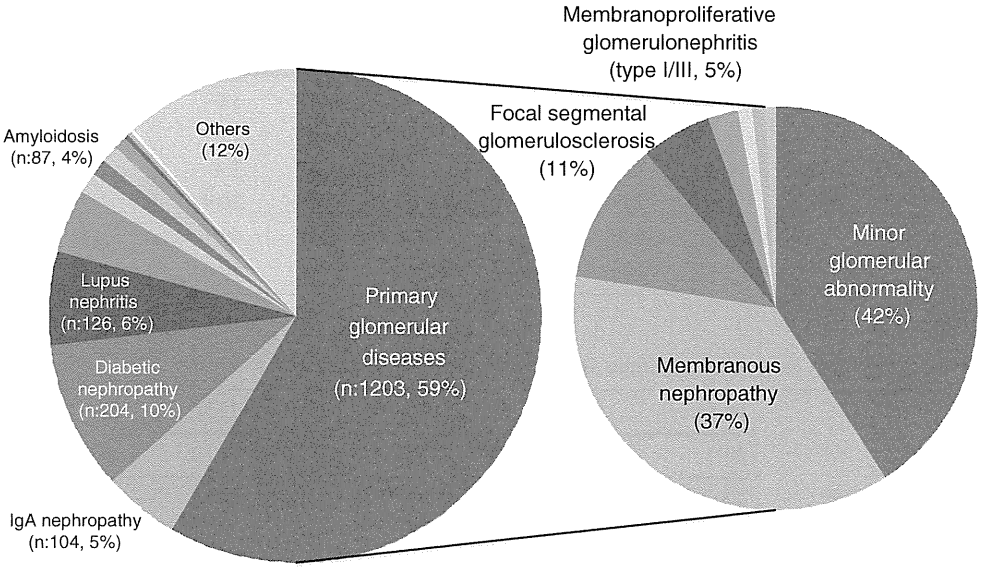

Fig. 4 Glomerular lesions of nephrotic syndrome patients in Japan. J-RBR 2007–2010 registry: 2066 cases in total; 1203 cases of primary glomerular disease. Membranous nephropathy accounted for 37% of the idiopathic nephrotic syndrome cases in Japan

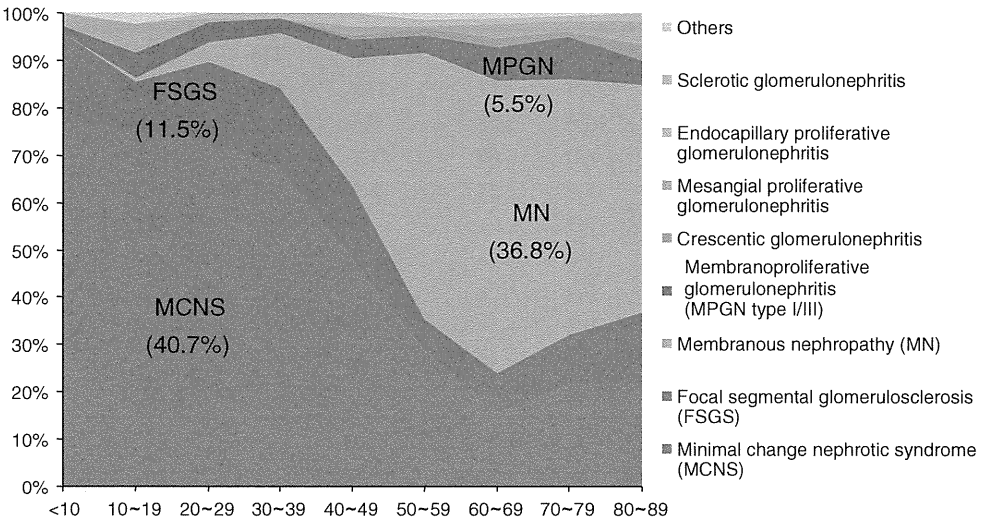

Fig. 5 Glomerular lesions of idiopathic nephrotic syndrome patients in Japan according to age. J-RBR 2007–2010 registry: 1203 cases of primary glomerular disease excluding IgA nephropathy

Age distribution of nephrotic syndrome and idiopathic membranous nephropathy patients in Japan

When we analyzed the 1,203 renal biopsy-proven nephrotic syndrome patients by age, the incidence of idiopathic MN gradually increased from the fourth decade and peaked in the seventh decade. Idiopathic MN was present in 48.3–61.9% of the primary nephrotic syndrome patients who were older than 50, and 57.6% of the 550 patients who were older than 60 (Fig. 5). In other words, 317 (71.6%) out of 443 idiopathic MN patients were aged over 60 years. A previous report found that being aged over 60 years was an independent risk factor for ESRF in Japanese idiopathic MN (hazard ratio 1.98; 95% cumulative interval 1.20–3.28; $p = 0.008$) [7]. In addition, being aged over 50 years, being male, daily proteinuria of more than 8.0 g, and an elevated serum creatinine level were also found to be independent risk factors for ESRF in North American idiopathic MN patients [1]. On the basis of these findings, half of Japanese idiopathic MN patients have risk factors for ESRF.

Conclusion

The J-RBR/J-KDR registry developed by the Japanese Society of Nephrology provides nationwide cohort data for epidemiological studies of MN. On the basis of our findings, half of nephrotic Japanese idiopathic MN patients have risk factors for ESRF, and 10% belong to the high-risk group. Further studies with high-grade evidence should resolve the natural history and therapeutic problems of idiopathic MN in elderly Japanese.

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Conflict of interest Three of the authors (HY, TT, and HS) have no conflicts of interest to disclose. One author (SH) was supported by Daiichi-Sankyo Co. Ltd.

Appendix

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ORIGINAL ARTICLE

Renal disease progression in autosomal dominant polycystic kidney disease

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Abstract
Background Autosomal dominant polycystic kidney disease is a lifelong progressive disorder. However, how age, blood pressure, and stage of chronic kidney disease (CKD) affect the rate of kidney function deterioration is not clearly understood.
Methods In this long-term observational case study up to 13.9 years (median observation period for slope was 3.3 years), serum creatinine was serially measured in 255 mostly adult patients. The glomerular filtration rate was estimated (eGFR) using a modified Modification of Diet in Renal Disease Study method. The total kidney volume (TKV) has been measured in 86 patients at one center since 2006.
Results As age increased, eGFR declined significantly ($P < 0.0001$), but the annual rate of decline of eGFR did not correlate with age or initially measured eGFR. In patients with CKD stage 1, eGFR declined at a rate which was not significantly different from other advanced CKD stages. Hypertensive patients had lower eGFR and larger TKV than normotensive patients at a young adult age. The slopes of regression lines of eGFR and TKV in relation to age were not different between high and normal blood pressure groups.
Conclusion The declining rate of eGFR was relatively constant and did not correlate with age or eGFR after adolescence. eGFR was already low in young adult patients with hypertension. As age increased after adolescence, eGFR declined and TKV increased similarly between normal and high blood pressure groups. eGFR starts to decline in patients with normal eGFR, suggesting that the decline starts earlier than previously thought.

Keywords Autosomal dominant polycystic kidney disease · Glomerular filtration rate · Kidney volume · Kidney function · Kidney failure

Introduction

Progressive deterioration of renal function and enlargement of renal cysts are two hallmarks of autosomal dominant polycystic kidney disease (ADPKD). It is widely recognized that during the renal compensation period, renal function decreases slowly but subsequently decreases at a relatively faster rate [1, 2]. In a three-year CRISP study [3], the rate of change in iothalamate clearance was faster in the older age group (>30 years) than in the younger group, but the difference was not statistically significant ($P = 0.2$). Even if the glomerular filtration rate (GFR) is maintained near normal at a young adult age, ADPKD patients already have decreased effective renal plasma flow and an increased filtration fraction [4]. A recent study revealed that occurrence of glomerular hyperfiltration in ADPKD children is associated with a significantly faster decline in renal function and higher rate of kidney enlargement over

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time [5]. As a result of more severe progression of ADPKD children with glomerular hyperfiltration, GFR is already lower than normal at around adolescent. Long-term longitudinal studies delineating renal disease progression are limited.

Currently, potential therapeutic interventions are being developed for ADPKD [6–11]. The potentially effective compounds examined so far seem not to reverse already decreased renal function or decrease already enlarged kidney volume but to mitigate progressive deterioration or enlargement [6–8, 11]. The mammalian target of rapamycin inhibitors, appeared to retard the growth of kidneys but not to slow functional deterioration in patients with ADPKD who have stage 2 or 3 chronic kidney disease (CKD) [8, 10]. Tolvaptan, a V2-specific vasopressin receptor antagonist, slowed cyst growth progression in ADPKD patients compared to historical controls [11]. In animal experiments, it was suggested that intervention with a V2-specific vasopressin receptor antagonist should be early in ADPKD [18].

It is not known how the declining rate differs between CKD stage 1 patients through to CKD stage 3 patients with ADPKD. It is important to delineate the characteristics of the natural course of disease progression in ADPKD when therapeutic intervention becomes feasible.

Materials and methods

Two hundred and fifty-five patients with ADPKD participated in an observation study at Kyorin University, Teikyo University and Hokkaido University from 1995 to 2009. The patients fulfilled Ravine's diagnostic criteria. The study was an observational case study measuring serum creatinine at least once a year and monitoring blood pressure. Serum creatinine was measured enzymatically. The estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) was calculated using the following formula: eGFR (male) = $194 \times Cr^{-1.094} \times Age^{-0.287}$, and eGFR (female) = eGFR (male) $\times$ 0.739. This equation is a Japanese coefficient for the modified Isotope Dilution Mass Spectrometry-Modification of Diet in Renal disease (IDMS-MDRD) Study [12]. The slopes of the reciprocal of serum creatinine concentration (1/Cr) were also examined. The slopes of eGFR (ml/min/1.73 m^2/year) and 1/Cr (dl/mg/year) were calculated when creatinine was measured for at least two points with an interval longer than 12 months. Slopes were calculated using linear regression analysis in each patient. The staging of kidney function is based on the K/DOQI Clinical Practice Guidelines on CKD [13].

Since 2006, total kidney volume (TKV) has been measured at Kyorin University Hospital in routine clinical practice by high-resolution magnetic resonance imaging using volumetric measurement of cross-sectional imaging, as described in the report from the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) [3, 14, 15]. Gadolinium enhancement was not used for safety concerns. The TKV slope is calculated using linear regression analysis and is expressed as the yearly change of TKV (ml/year).

In the present study, hypertension is defined as high blood pressure requiring the use of anti-hypertensive agents. In the three hospitals where the study was conducted, blood pressure >130/85 was commonly treated by renin–antiotensin system blockers to achieve the target blood pressure.

For evaluation of the relationship between eGFR and TKV, data were analyzed when eGFR and TKV were measured within 1 month. As eGFR and TKV were measured several times in one patient, initial measurement data were used to examine age-related changes of eGFR and TKV. This protocol was approved by an institutional review board, and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent to use their clinical data for medical research.

Statistical analyses

Analyses were performed with Microsoft Excel 2003, SAS 9.1 for Windows. Parametric variables are expressed as the mean ± standard deviation. Two-sided $P < 0.05$ was considered to indicate statistical significance. P values for differences between CKD stages were obtained using ANOVA or the Kruskal–Wallis test. Correlations between two variables were examined by linear regression analysis. The correlation coefficient (r) was obtained by the Spearman rank-order correlation coefficient. The relations of two linear regression lines between normotensive and hypertensive groups were compared by F test. Student's t test was used to calculate the P value between two age groups.

Results

Pertinent data in groups according to the measured parameters are shown in Table 1. eGFR was measured in 255 patients and eGFR slope was calculated in 196 patients whose eGFR was measured more than twice and more than 12 months apart. TKV was measured in 86 patients and the TKV slope was calculated in 46 patients.

Initially measured eGFR in relation to age is shown in Fig. 1. eGFR decreased statistically significantly as age increased ($P < 0.0001$).

The change in eGFR per year (eGFR slope) was plotted against age and initially measured eGFR in 196 patients

Table 1 Pertinent data on kidney function and volume according to the measured parameters

Data	Groups according to the measured parameters			
	eGFR[a]	eGFR slope[c]	TKV[b]	TKV slope[c]
Patient number	255	196	86	46
Male/female	99/156	80/116	34/52	18/28
Age (years)	44.9 ± 14.2	46.0 ± 13.8	47.0 ± 14.2	45.1 ± 14.5
Mean observation period (years)	3.3 ± 3.1	4.2 ± 3.0	0.8 ± 0.8	1.4 ± 0.5
Median observation period (years)	2.5	3.3	0.8	1.3
AntiHTN Tx/no antiHTN Tx[a]	184/71	153/43	67/19	35/11
eGFR (ml/min/1.73 m^2)[b]	62.4 ± 37.0	61.2 ± 33.1	63.4 ± 32.1	71.5 ± 29.4
eGFR slope[c] (ml/min/1.73 m^2/year)	–	−3.4 ± 4.9	–	–
eGFR slope/initial eGFR (%/year)	–	−7.4 ± 8.9	–	–
1/Cr slope (dl/mg/year)	–	−0.05 ± 0.08	–	–
TKV (ml)	–	–	1839.4 ± 1329.2	1675.0 ± 944.4
TKV slope[c] (ml/year)	–	–	–	86.8 ± 161.6
TKV slope/initial TKV (%/year)	–	–	–	5.6 ± 8.8
Log TKV slope[d] (log ml/year)	–	–	–	0.02 ± 0.04
Log TKV slope/initial log TKV (%/year)	–	–	–	0.7 ± 1.2
Observation period of TKV slope (years)	–	–	–	1.4 ± 0.5

TKV total kidney volume

[a] AntiHTN Tx/no antiHTN Tx: patient number with and without anti-hypertensive treatment. HTN Tx is indicated for BP higher than 130/85 mmHg

[b] eGFR is estimated GFR measured the first time

[c] Slope is the annual change of eGFR or TKV

[d] Log TKV slope is log (TKV2/TKV1)/year

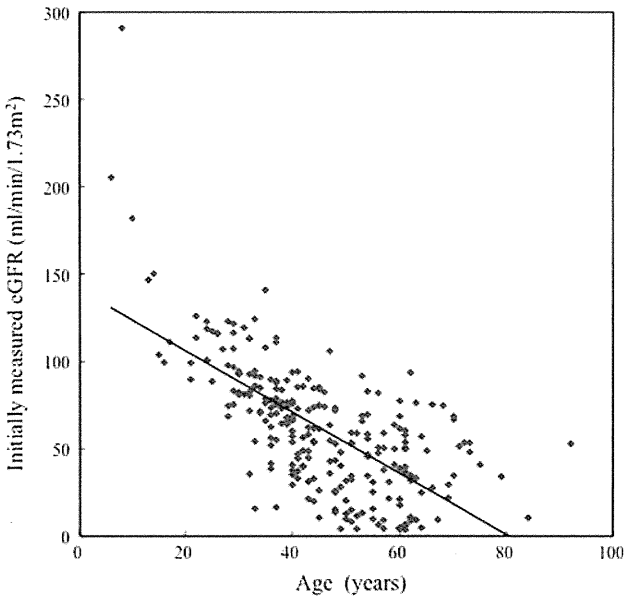

Fig. 1 Initially measured eGFR distribution in relation to age ($n = 255$). $y = -1.757x + 141.28$, $r = -0.6871$, $P < 0.0001$

(Fig. 2a, b). The regression lines were not statistically significant. The result suggests that eGFR slope does not relate to age or initially measured eGFR.

In Table 2, 196 patients are grouped according to the CKD stage [13] depending on the initially measured eGFR. The advancement of CKD stages significantly related to increased age ($P < 0.0001$). Slopes of eGFR and 1/Cr were not statistically different among CKD stages, and even younger patients with relatively preserved kidney function in stage 1 had similar slopes of eGFR and 1/Cr to patients in advanced stages. The percent ratio of the decline in eGFR and 1/Cr in relation to the initially measured values progressively increased as the CKD stage advanced ($P < 0.0001$).

1/Cr was plotted against age in 106 patients who had been followed for more than 3 years (Fig. 3). In the supplementary figure, the plot of 1/Cr versus age is illustrated in all 255 patients. 1/Cr declined to a greater or lesser extent every year with a relatively constant decline rate for each patient at considerable variance among individuals. Neither figure shows that 1/Cr remains stable at a younger age than at an older age. For more detailed examination of the compensatory period of GFR, eGFR is plotted against age in 36 patients who had been followed up for more than 5 years (Fig. 4). Similar to 1/Cr, eGFR declined in each patient. In five patients shown by red lines, the declining curve changed from moderate to rapid during follow-up. The change points did not show any age or eGFR level dependency.

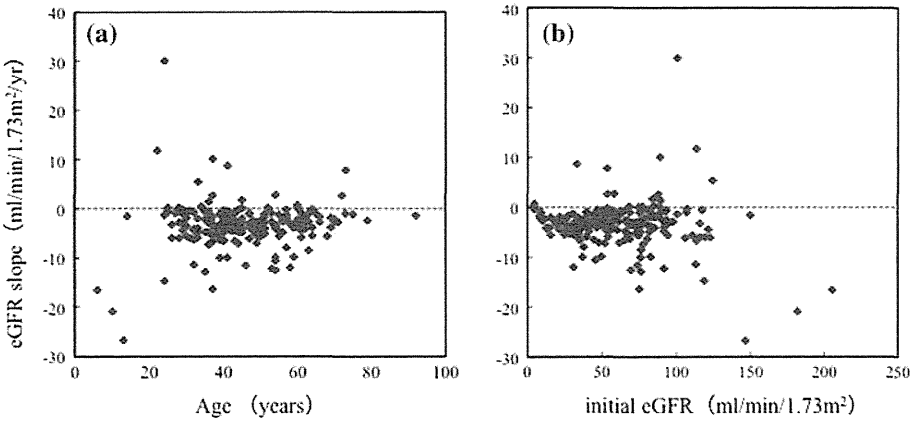

Fig. 2 Relationship of eGFR slope to age (**a**) and initial eGFR (**b**) ($n = 196$). **a** Spearman's rank correlation coefficient (r) = 0.0728, $P = 0.3094$. **b** Spearman's rank correlation coefficient (r) = −0.0412, $P = 0.5654$. No significant relationship is seen between eGFR slope and age, or between eGFR slope and initially measured eGFR. Mean observation time of eGFR was 4.2 ± 3.0 years

Table 2 Age, eGFR slope and 1/Cr slope in relation to the CKD stages of initially measured eGFR

	CKD stages according to initially measured eGFR[a] (ml/min/1.73 m^2)				*P* value
	Stage 1 ≥90	Stage 2 89–60	Stage 3 59–30	Stage 4 + 5[b] ≤29	
Initial eGFR (ml/min/1.73 m^2)	113.8 ± 25.9	75.1 ± 7.9	45.0 ± 8.8	16.3 ± 8.0	–
Patient number	32	62	71	31	–
Age (years)	29.9 ± 11.4	42.4 ± 10.2	52.4 ± 12.1	55.0 ± 8.4	<0.0001
eGFR slope[c] (ml/min/1.73 m^2/year)	−4.2 ± 9.5	−3.5 ± 4.1	−3.1 ± 3.3	−2.8 ± 1.7	0.6775
eGFR slope/initial eGFR × 100 (%/year)	−3.2 ± 8.0	−4.8 ± 5.4	−7.5 ± 8.5	−16.4 ± 10.3	<0.0001
1/Cr slope[d] (dl/mg/year)	−0.04 ± 0.13	−0.05 ± 0.07	−0.06 ± 0.07	−0.05 ± 0.03	0.8982
1/Cr slope/initial 1/Cr × 100 (%/year)	−2.2 ± 7.4	−4.0 ± 5.1	−6.7 ± 8.1	−15.1 ± 9.6	<0.0001

Data are presented as the mean ± SD. *P* values are calculated by ANOVA

[a] Patients were staged according to the National Kidney Foundation Disease Outcomes Quality Initiative guidelines

[b] ESRD (dialysis and transplantation) is not included in stage 4 and 5 groups

[c] eGFR slope is the annual change of estimated GFR

[d] 1/Cr slope is the annual change of 1/Cr

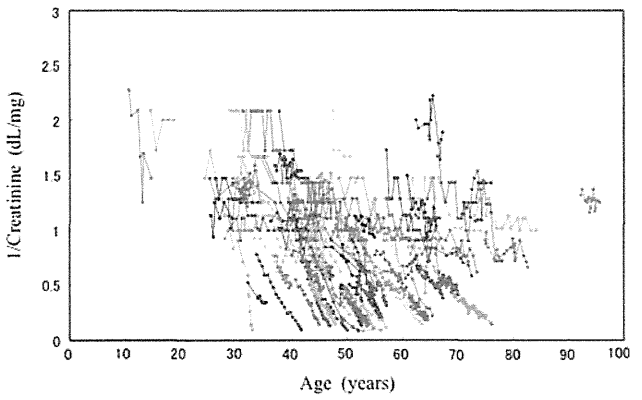

Fig. 3 1/Cr is plotted against age in 106 patients who had been followed up for more than 3 years. 1/Cr declines in most patients at an individually variable rate. Pattern of decline appears not to be age-dependent

The effects of age on the eGFR and TKV slopes are examined in Table 3. Forty-six patients whose TKV slopes were measured were divided into younger or older age groups for comparison purposes. Between the two groups, the difference in eGFR was statistically significant but differences in the eGFR slope, 1/Cr slope, TKV or TKV slope were not significant.

The initially measured eGFRs and log-transformed TKV are plotted against age in normotensive and hypertensive patients in Fig. 5a, b, respectively. In both figures, the regression lines for normotensive and hypertensive patients were not considered to be identical, with different *y*-intercepts, since there was a significant difference ($P < 0.01$, F test) in the *y*-intercept of the two regression lines under the null hypothesis that the *y*-intercept of the two lines was equal. There was no significant difference ($P = 0.6061$ in Fig. 5a or $P = 0.6079$ in Fig. 5b, F test) in the slope of the two lines under the null hypothesis that the slope of the two lines was equal.

Table 4 shows that in young adult patients aged <36 years, eGFR was lower and TKV was larger in the hypertensive group than in the normal blood pressure group.

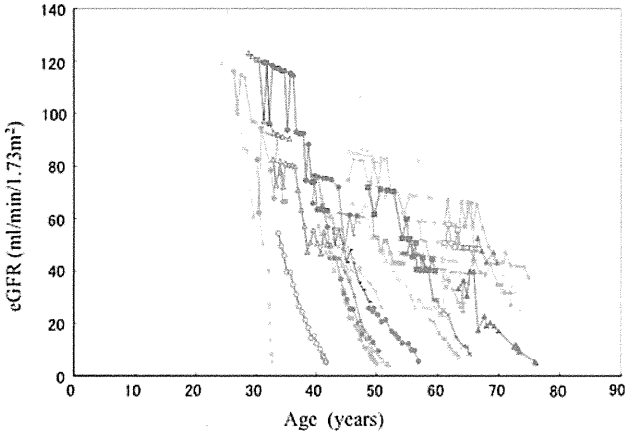

Fig. 4 eGFR changes in patients followed for more than 5 years ($n = 36$). In 5 patients shown by a *red line*, the declining curve changed from moderate to rapid during follow up. The change points varied in relation to age or eGFR level. Other patients are shown in *blue* for easy identification

Discussion

ADPKD is the most common hereditary kidney disease. The disease is characterized by the formation of numerous kidney cysts and their development, leading to kidney enlargement and failure, reaching end-stage renal failure in up to about 50% by age 70 [16].

Polycystic kidney disease animal model studies suggested that earlier intervention resulted in more effective prevention of disease progression [17, 18]. The potential candidates clinically examined so far seem to attenuate progression but not to reverse progressed renal disease [6–8, 11]. Thus, it is a crucial issue when to start treatment intervention.

The present study confirmed that renal function decreased progressively as a function of age [1, 3, 16, 19, 20]. In 196 patients with a mean age >30 years, the mean eGFR slope was -3.4 ± 4.9 ml/min/1.73 m^2/year. In 46 patients with mean TKV >1500 ml, the TKV slope was 86.8 ± 161.6 ml/year (5.6 ± 8.8%/year) (Table 1). The present data of eGFR and TKV slopes are compatible with previous findings [3, 10]. The slopes of GFR (measured by iothalamate clearance) and TKV were analyzed according to TKV and age groups in the CRISP study [3]. Analysis of variance revealed that the slopes of GFR differed among subgroups with different initial TKV ($P = 0.005$), whereas the slopes of GFR did not differ significantly among subgroups with different initial ages ($P = 0.20$); there was no significant interaction between TKV and age ($P = 0.95$) [3]. In the present study, the eGFR slope was less in the older group than younger group (Table 3), but the difference was not statistically significant ($P = 0.154$). In addition, there was no significant relationship between age and eGFR slope (Fig. 2a). Both the present and CRISP study [3] suggest that the eGFR slope is not significantly affected by age, at least after adolescence.

The MDRD equation for estimating GFR is widely used [8–10] but its accuracy was recently reported to be 83% in ADPKD patients [21]. Renal function changes are qualitatively reflected by the 1/Cr slope in individual subjects, because individual body muscle volume and hydration status are relatively stable in most patients, at least for relatively short periods of a few years. In the present study, the 1/Cr slope was analyzed in addition to the eGFR slope and the results were qualitatively similar in both analyses (Tables 2, 3; Figs. 3, 4).

In 5 of 36 patients followed for more than 5 years, renal disease progression accelerated during observation (Fig. 4). This acceleration did not seem to be related to age or eGFR level, but presumably to individually different causes, including infection, hematuria, obstruction by urolithiasis or other events. If the acceleration of renal disease progression is due to the end of the renal

Table 3 Comparison of the slopes of eGFR and TKV between the two age groups

	Younger group	Older group	*P* value
Age group (years)	13–41	42–75	
Mean age (years)	34 ± 6.4	57 ± 10.5	
Male/female	11/12	7/16	
eGFR (ml/min/1.73 m^2)	87.0 ± 29.5	55.9 ± 19.7	<0.0001
eGFR slope (ml/min/1.73 m^2/year)	−4.6 ± 7.3	−2.1 ± 3.1	0.1540
eGFR slope/initial eGFR (%/year)	−4.2 ± 9.2	−4.4 ± 7.6	0.9640
1/Cr slope (dl/mg/year)	−0.06 ± 0.10	−0.03 ± 0.06	0.3876
1/Cr slope/initial 1/Cr × 100 (%/year)	−3.0 ± 8.1	−3.8 ± 7.1	0.7535
TKV (ml)	1509.3 ± 874.3	1840.8 ± 1001.2	0.2381
TKV slope (ml/year)	110.2 ± 207.5	63.5 ± 96.0	0.3326
TKV slope/initial TKV (%/year)	7.6 ± 10.3	3.6 ± 6.6	0.1215
Log TKV slope (log ml/year)	0.03 ± 0.04	0.01 ± 0.03	0.1877
Log TKV slope/initial log TKV (%/year)	0.9 ± 1.4	0.4 ± 1.0	0.1580

Forty-six patients whose TKV slopes were measured were divided into younger and older age groups for comparison. Data are the mean ± SD. *P* values were calculated by Student's *t* test

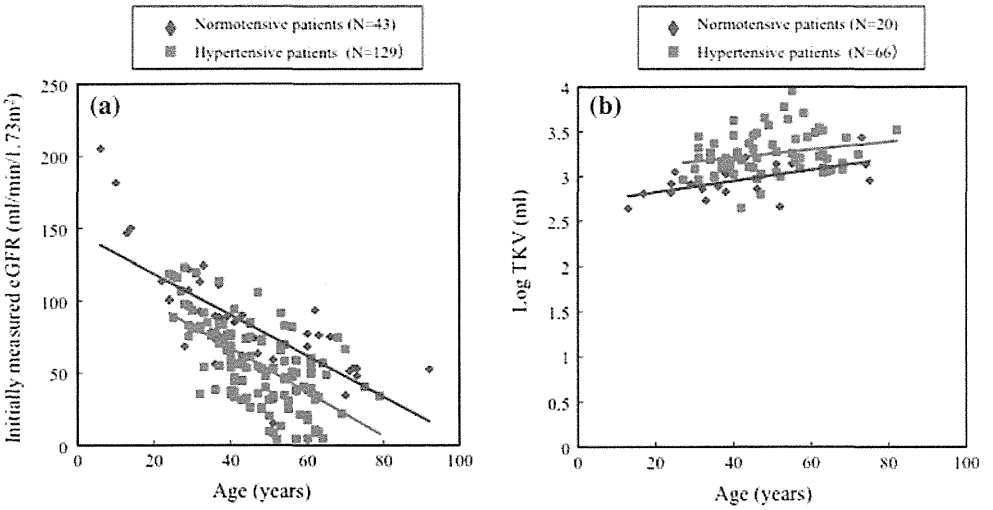

Fig. 5 **a** Initially measured eGFRs are plotted against age in normotensive (*blue*) and hypertensive (*red*) patients. Regression analysis for normal blood pressure group: $y = 151.08 - 1.546x$ (where y = eGFR and x = age, $r = -0.7791$, $P < 0.0001$, $n = 70$) and that for hypertensive group: $y = 132.30 - 1.666x$ ($r = -0.6587$, $P < 0.0001$, $n = 158$). **b** The relationship between age and log-transformed TKV in normotensive (*blue*) and hypertensive (*red*) patients. Regression analysis for normal blood pressure group; $y = 2.7003 + 0.006275x$ (where y = log TKV and x = age, $r = 0.57859$, $P = 0.0075$, $n = 20$) and that for hypertensive group; $y = 3.0339 + 0.004452x$ ($r = 0.23144$, $P = 0.0615$, $n = 66$). In both **a** and **b**, the regression lines for normotensive and hypertensive patients were not considered to be identical, with different y-intercepts, since there was a significant difference ($P < 0.01$, F test) in the y-intercept of the two regression lines under the null hypothesis that the y-intercept of two lines was identical. There was no significant difference ($P = 0.6061$ in **a** or $P = 0.6079$ in **b**, F test) in the slope of the two lines under the null hypothesis that the slope of the two lines was identical

compensation mechanism, the terminal points of the compensation mechanism might be heterogeneous among ADPKD patients.

In relatively younger adult (29.9 ± 11.4 years) patients whose renal function was retained (CKD stage 1 in Table 2), the eGFR slope was already negative. In the majority of patients with initially measured eGFR >90 ml/min/1.73 m^2, the eGFR slope was negative, as shown in Fig. 2b. These results suggest that the renal compensation mechanism might terminate in the second decade of life in most patients with ADPKD.

A recent study which examined the detailed renal functions of young ADPKD patients showed abnormal kidney function even in the younger generation [4]. In a quartile of the younger age group (27 ± 5 years) in that study, GFR decreased but was statistically not different from that of the normal healthy controls. Even in these younger age group patients, effective renal plasma flow sharply decreased. Patients with CKD stage 1 (Table 2) in the present study correspond to quartile 1 group patients in that study [4], because age (29.9 ± 11.4 vs 27 ± 5 years) and eGFR (113.8 ± 25.9 ml/min/1.73 m^2) in the present study and GFR measured by iothalamate clearance (117 ± 32 ml/min) were not statistically different. The present study shows a negative eGFR slope and the study [4] showed decreased renal plasma flow in similar younger adult patients who maintained apparently normal GFR.

Table 4 Comparison of eGFR and TKV between normal and high blood pressure groups in young adults (≤35 years)

	Normotensive group	Hypertensive group	*P* value
N	36	27	
Initial BP[a]			
Systolic (mmHg)	117.9 ± 15.1	148.1 ± 14.2	<0.0001
Diastolic (mmHg)	68.5 ± 6.9	85.9 ± 13.7	0.0001
Post-Tx BP[b]			
Systolic (mmHg)	115.8 ± 14.4	128.4 ± 12.9	0.0030
Diastolic (mmHg)	70.5 ± 11.6	78.4 ± 6.5	0.0066
eGFR (ml/min/1.73 m^2)	113.6 ± 42.5	86.6 ± 24.2	0.0044
N	10	12	
TKV (ml)	826.3 ± 319.2	1713.2 ± 675.6	0.0011

Data are the mean ± SD. *P* values were calculated by Student's *t* test

[a] Initial BP is blood pressure without anti-hypertensive treatment in hypertensive group and blood pressure at initial visit in normotensive group

[b] Post-Tx BP is blood pressure at the study time. In hypertensive group, all patients were receiving antihypertensive medication

Initially measured eGFR in relation to age in hypertensive patients was lower than that in normotensive patients, and the present results indicated that differences in eGFR between the two groups had already occurred before age 36 (Fig. 5a; Table 4). Hypertensive children

with ADPKD were reported to be at particular risk for increases in renal volume and decreased renal function as compared with children with normal blood pressure. Renal function was already decreased by age 20, at least in hypertensive children [20]. The important finding in the present study is that declining rates of eGFR and increasing rates of TKV are not significantly different between normal blood pressure and high blood pressure patients after around 20 years. This phenomenon might or might not be due to anti-hypertensive treatment. The results of previous [20] and present studies suggest that renal functional deterioration starts far earlier than 20 years of age, especially in hypertensive ADPKD patients.

The potential limitations of this study include retrospective analysis, use of eGFR and 1/Cr, as well as an ethnically homogenous patient population in Japan, and hence it may not be applicable to other ethnicities.

Conclusions

In conclusion, eGFR starts to decline in young adult patients with apparently normal eGFR. After adolescence, the declining rate of eGFR is relatively constant and does not relate to age or GFR. Hypertensive patients had lower eGFR and larger TKV than normotensive patients at young adult age. After adolescence, eGFR declined at a similar rate between normotensive and hypertensive groups. A long-term longitudinal study starting in childhood is necessary to more thoroughly understand the characteristics of disease progression in ADPKD.

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Conflict of interest Dr. Higashihara serves as consultant to Otsuka Pharmaceutical.

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ORIGINAL ARTICLE

Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan

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Abstract
Background The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database of the Japanese Society of Nephrology started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record the pathological, clinical, and laboratory data of renal biopsies in 2007.
Methods The patient data including age, gender, laboratory data, and clinical and pathological diagnoses were recorded on the web page of the J-RBR, which utilizes the system of the Internet Data and Information Center for Medical Research in the University Hospital Medical Information Network. We analyzed the clinical and pathological diagnoses registered on the J-RBR in 2007 and 2008.
Results Data were collected from 818 patients from 18 centers in 2007 and 1582 patients from 23 centers in 2008, including the affiliated hospitals. Renal biopsies were obtained from 726 native kidneys (88.8%) and 92 renal grafts (11.2%) in 2007, and 1400 native kidneys (88.5%) and 182 renal grafts (11.5%) in 2008. The most common clinical diagnosis was chronic nephritic syndrome (47.4%), followed by nephrotic syndrome (16.8%) and renal

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transplantation (11.2%) in 2007. A similar frequency of the clinical diagnoses was recognized in 2008. Of the native kidneys, the most frequent pathological diagnosis as classified by pathogenesis was immunoglobulin (Ig) A nephropathy (IgAN) both in 2007 (32.9%) and 2008 (30.2%). Among the primary glomerular diseases (except IgAN), membranous nephropathy (MN) was the most common disease both in 2007 (31.4%) and 2008 (25.7%). *Conclusions* In a cross-sectional study, the J-RBR has shown IgAN to be the most common disease in renal biopsies in 2007 and 2008, consistent with previous Japanese studies. MN predominated in the primary glomerular diseases (except for IgAN). The frequency of the disease and the clinical and demographic correlations should be investigated in further analyses by the J-RBR.

Keywords Glomerulonephritis · Tubulointerstitial disorder · Renal vascular disease · Renal grafts · National registry

Introduction

There has been no national registry of renal biopsies in Japan. The Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for Renal Biopsy Database in the Japanese Society of Nephrology established the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data regarding all renal biopsies performed in 2007.

To date, the epidemiological and clinical data of renal diseases are available from nationwide registries of renal biopsies from the United Kingdom [1], Italy [2], Denmark [3], Spain [4], the Czech Republic [5], and Australia [6]. The role of a renal biopsy registry has been recently encouraged [7]. In Japan, several surveys were temporarily conducted for patients with restricted renal diseases, including primary glomerulonephritis [8], idiopathic membranous nephropathy (MN) [9], and immunoglobulin (Ig) A nephropathy (IgAN) [10]. However, there has been no web-based, nationwide, or prospective registry system of overall renal biopsies in Japan. The aim of the current study was to provide data to investigate the epidemiology and frequency of renal diseases with a histological diagnosis for patients registered in 2007 and 2008 on the J-RBR.

Subjects and methods

Registry system and patients

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