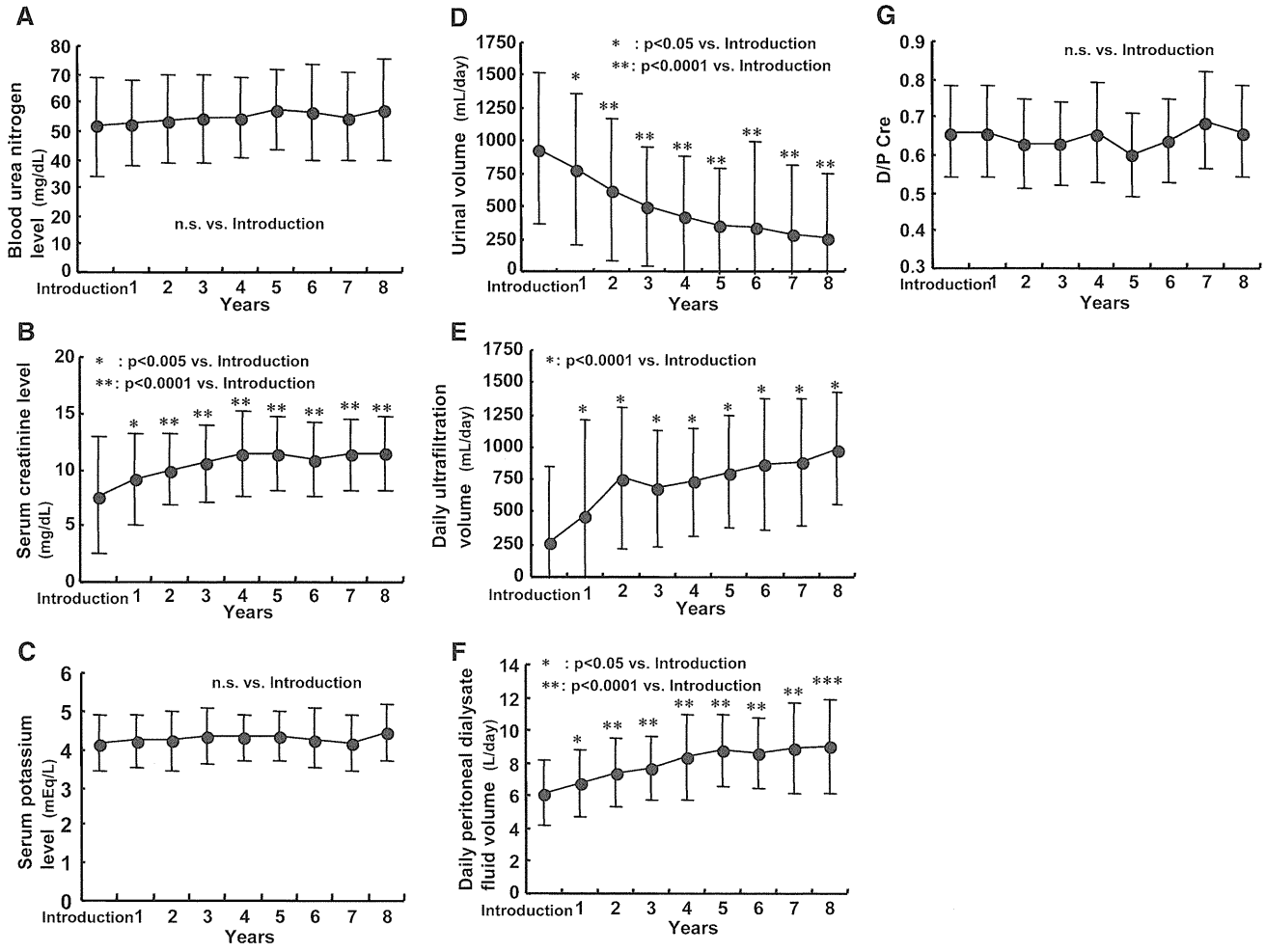

Fig. 4 Residual renal function, status of peritoneal dialysis (*PD*) and peritoneal function in PD patients from 2005 to 2007. **a** Levels of blood urea nitrogen (*BUN*) and **b** creatinine are shown as markers of renal function. **c** Serum potassium level. **e** Changes in ultrafiltration and **g** dialysate-to-plasma creatinine concentration ratio (*D/P Cre*) are shown as markers of peritoneal function. **d** Changes in urinary volume and **f** amount of peritoneal dialysis fluid are also shown. Each value represents mean ± SD

A list of identified microorganisms is shown in Table 6. Identification of microorganisms was achieved in 68.2% of cases with PD-related peritonitis, while culture-negative results were obtained for 31.8%. Most cases of infectious peritonitis were caused by a single microorganism, but 14.9% of all cases involved multiple-organism infection. The highest incidence rates were seen for Gram-positive cocci (42.7%) (Table 6), principally involving *Staphylococcus* sp. and *Streptococcus* sp. (21.5 and 12.8%, respectively).

Seven of 154 patients died due to peritonitis, with causative microorganisms of coagulase-negative *Staphylococcus,* methicillin-resistant *Staphylococcus aureus*, *Serratia marcescens*, *Enterobacter aerogenes*, and *Candida guilliermondii* for 1 patient each and an unidentified microorganism for 2 patients.

When we examined age, gender, usage of any device for PDF bag change, DM or non-DM, CAPD or APD, and catheter insertion methods as risk factors, incidence of peritonitis was significantly higher in patients >65 years old and in women according to multivariate analysis, but no relationships to other factors were identified (Table 7).

Excluding PD-related infectious diseases, incidence of other complications associated with PD therapy are shown in Table 8.

Discussion

First, we have shown a profile of patient characteristics and changes in average laboratory data according to the duration of PD therapy after induction for 13 institutions in the Tokai area of Japan. Although the prevalence of PD patients has not recently increased in Japan [7], the present study showed that the prevalence of ESRD patients on PD therapy gradually increased over 3 years in our area. Most

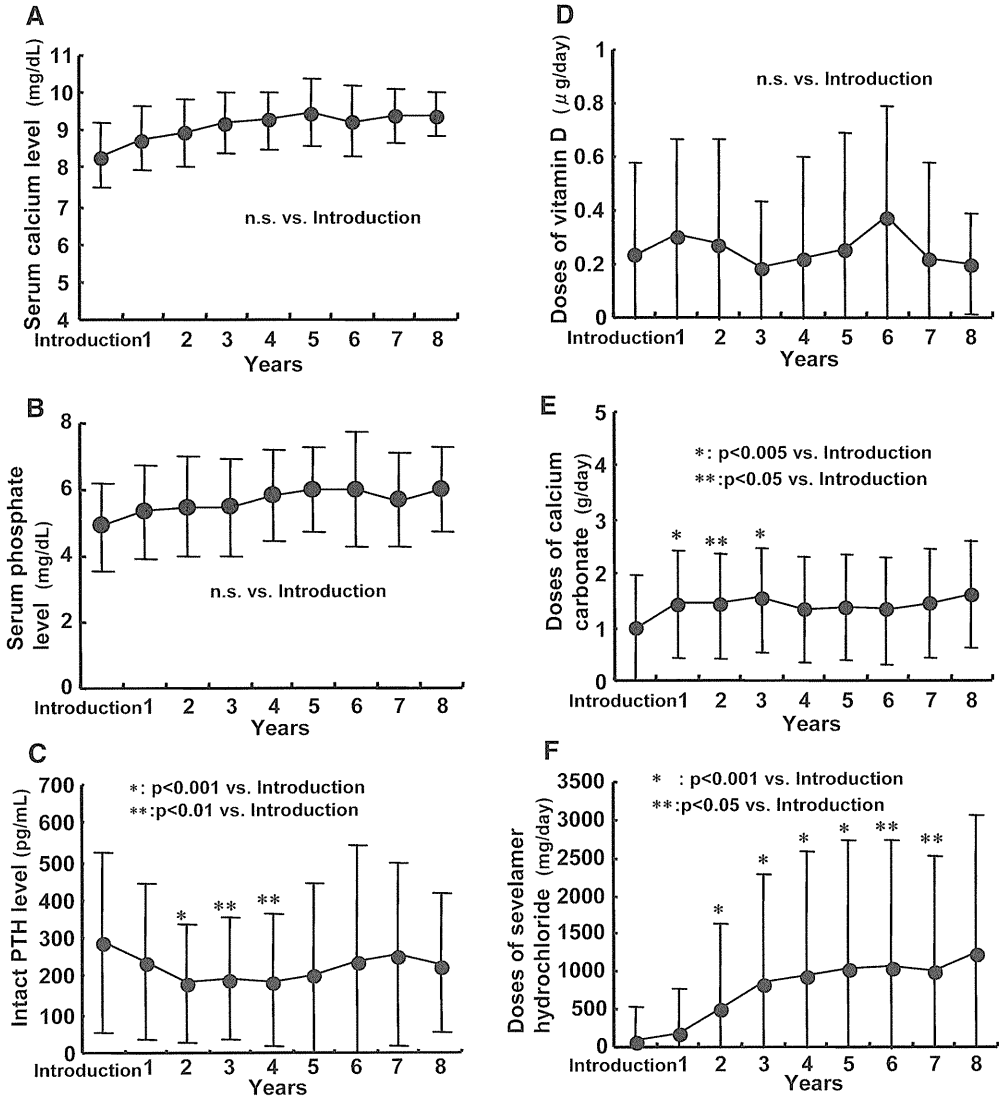

Fig. 5 Calcium metabolism and doses of related agents in peritoneal dialysis (*PD*) patients from 2005 to 2007. Levels of **a** calcium, **b** phosphate, and **c** intact parathyroid hormone (*iPTH*), and **d** active vitamine D, **e** doses of calcium carbonate, and **f** sevelamer hydrochloride. Each value represents mean ± SD

laboratory data showed no significant changes during our observation. Monthly usage of erythropoietin tended to show a slight increase year-by-year. Decreased UV and increased serum creatinine level were observed annually. Mean D/P Cre did not change significantly during our observations. D/P creatinine levels might have been well preserved because patients on long-term PD might have achieved good control, while patients showing poor control on PD therapy might have been withdrawn in the early phase. Mean levels of serum calcium, phosphate, and iPTH were relatively preserved. Dose of calcium carbonate as a phosphate binder was initially able to be increased, but needed to be decreased after the third year and additional administration of sevelamer hydrochloride as another phosphate binder was required as an alternative phosphate binder to control hyperphosphatemia. These results suggest that control of calcium metabolism deteriorates over time, supporting the notion that residual renal function is associated with good regulation of serum iPTH level [11].

Second, we performed detailed analyses regarding the withdrawal of patients from PD therapy to clarify factors suppressing the prevalence of PD patients. One severe complication in PD therapy is EPS, which has poor prognosis and occurs in ESRD patients on long-term PD therapy [12]. Fear of EPS might be one reason Japanese physicians avoid choosing PD therapy as a renal replacement therapy (RRT). However, approximately half of the patients withdrawn from PD therapy in our survey were withdrawn within 3 years after PD introduction. Even if we focused on the 308 incidental patients from 2005 to 2007, 39.3% were still withdrawn within 3 years after introduction, showing worse results than the 6.9% in a Hong Kong

Table 6 Microorganisms causing peritoneal dialysis (PD)-related peritonitis over 3 years

Group of microorganism	*n* (%)
Gram-positive cocci	117 (42.7)
Staphylococcus sp.	59 (21.5)
MSSA	9 (3.3)
MRSA	17 (6.2)
Staphylococcus epidermidis	20 (7.3)
Other CNS	13 (4.7)
Streptococcus sp.	35 (12.8)
Enterococcus sp.	8 (2.9)
Micrococcus sp.	9 (3.3)
Others	6 (2.2)
Gram-positive rods	8 (2.9)
Bacillus sp.	4 (1.4)
Corynebacterium sp.	3 (1.1)
Arcanobacterium haemolyticum	1 (0.4)
Gram-negative rods	51 (18.6)
Pseudomonas sp.	14 (5.1)
Escherichia coli	6 (2.2)
Enterobacter sp.	6 (2.2)
Seratia sp.	6 (2.2)
Klebsiella sp.	5 (1.8)
Acinetobacter sp.	5 (1.8)
Others	9 (3.3)
Tuberculosis	2 (0.7)
Fungus	9 (3.3)
Culture negative	87 (31.8)

MSSA methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *CNS* coagulase-negative *Staphylococcus*

Table 7 Predictors of peritoneal dialysis (PD)-related peritonitis

Factor	*P*	OR	95% CI
Age ≥65 years	0.014*	0.617	(0.420–0.908)
Female gender	0.049*	1.517	(1.002–2.296)
DM/non-DM	0.309	0.810	(0.540–1.215)
Device +/−	0.243	1.284	(0.844–1.952)
CAPD/APD	0.506	1.156	(0.754–1.771)
Non-embedding/embedding	0.556	0.875	(0.560–1.365)

OR odds ratio, *95% CI* 95% confidence interval, *DM* diabetes mellitus, *CAPD* continuous ambulatory PD, *APD* automated PD, *non-embedding* traditional PD catheter insertion technique, *embedding* Moncrief–Popovich technique of embedding PD catheter

* $p < 0.05$

study [3], 27.4% in a Korean study and 36.5% in a Swedish study [13]. A previous Japanese report showed that the technical 5-year survival rate was over 50%, based on

Table 8 Peritoneal dialysis (PD)-related complications other than PD-related infectious diseases for 3 years

Complication	*n* (% in 561 patients)
Catheter obstruction which was wrapped by omentum	7 (1.2)
Hydrothorax by defects in the diaphragm	6[b] (1.1)
Inguinal hernias	19 (3.4)
Abdominal wall hernia	9[a] (1.6)
Total	41 (7.2)

[a] 7 of 9 represented umbilical hernia

[b] 1 of 6 diaphragm penetrations occurred on the left side

results from PD centers with large numbers of PD patients [6]. In the present observations, prevalence increased, although early withdrawals comprised more than half of the total withdrawals. As the prevalence of PD patients has not been increasing in Japan overall, many PD patients in this country might be withdrawn early after PD induction. As PD-related peritonitis was the most common reason for withdrawal, as in other countries [14], we focused on and analyzed factors associated with PD-related peritonitis. In the present study, 8.8% of all deaths and 26.7% of all transfers to HD were caused by peritonitis and mean incidence of peritonitis was 1 episode/42.6 patient-months. Incidences of peritonitis in other Asian countries have been reported as ranging from 1 episode/19.46 patient-months to 1 episode/71 patient-months [15]. A report from the UK showed an incidence of peritonitis of 1 episode/14.7 patient-months for CAPD and 1 episode/18.1 patient-months for APD [16]. A recent study from a US group performed in multiple centers around the world found a median incidence for peritonitis of 1 episode/26 patient-months [17]. Those reports indicate that our incidence of PD-related peritonitis is not unusual compared with other countries. In contrast, the latest Japanese report showed an incidence of 1 episode/73.5 patient-months, based on a survey of centers with >20 PD patients [5], which is a much better result than in our survey. This discrepancy might have resulted from the expertise of Japanese medical centers with large numbers of well-controlled PD patients. The prognosis of PD therapy is reportedly better in centers with >20 PD patients [18, 19]; however, many medical clinics and hospitals in Japan treat only a small number of PD patients (<10 patients). Decreasing the early withdrawal rate from PD therapy might be important, as many patients who have chosen PD therapy might wish to continue PD therapy as long as they safely can. Institutional education and support systems for PD patients to improve PD prognosis might have been developed in medical institutions with large numbers of PD patients, representing

a 'center effect', but not in clinics with small numbers of PD patients [18, 19]. The incidence of peritonitis from our survey, which involved clinics and hospitals with small numbers of PD patients, might more closely mirror the overall situation for Japanese PD patients, differing from previous Japanese reports [4]. This may be an important point to consider in attempts to decrease early withdrawal from PD therapy.

As Gram-positive cocci were the most common bacteriological cause of PD-related peritonitis in the present study, technical problems, particularly contamination during PD bag exchanges, might be a major issue in our area, similar to other countries [15, 20]. Notably, culture-negative results comprised up to 31.8% of results in our area, worse than the recommendation in the recent ISPD guidelines/recommendations that culture-negative results should represent <20% [9, 10]. Improving the education system for ESRD patients, particularly with regard to bag exchanges, and providing support systems through medical staff may thus improve the number of patients withdrawing early from PD therapy [21, 22]. Another important goal is to decrease of the rate of culture-negative peritonitis, as optimal antibiotic selection is difficult without accurate identification and empiric antibiotics must be selected for culture-negative peritonitis. In addition, social problems related to patients and/or their families represented another important reason for early withdrawal from PD therapy. These results suggest the importance of providing adequate information for ESRD patients and their families to facilitate the selection of RRT, improving device systems and constructing systems to support PD patients with their families.

In our survey, the technical survival rate of incidental PD patients from 2005 to 2007 was significantly worse among DM patients than among non-DM patients, similar to most studies on the prognosis of DM and non-DM patients on PD therapy [23]. In recent reports, icodextrin solution played a role in improving body fluid management for DM patients on PD [24–26]. Our results likewise suggest that DM patients might require use of icodextrin solution to improve body fluid control more than non-DM patients.

Our observations suggest early withdrawal as an important reason why the population of PD patients has not increased in Japan, with peritonitis as the biggest reason for early withdrawal from PD therapy. Improvements in education and training programs for both patients and medical staff might be necessary and patient support systems aimed at improving the incidence of peritonitis may prove helpful. Decreasing culture-negative peritonitis is also important for improving the prognosis of PD-related peritonitis. The present results, including the incidence of PD-related complications, might support the provision of better information to choose adequate RRTs for ESRD patients and to improve education of patients on PD therapy in Japan.

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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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for Renal Biopsy Database in the Japanese Society of Nephrology participated in this study. The report includes the data from patients on the J-RBR, registered prospectively from January to December of 2007 and 2008. Patient data including age, gender, laboratory data, and the clinical and pathological diagnoses were electronically recorded at each institution and registered on the web page of the J-RBR utilizing the system of Internet Data and Information Center for Medical Research (INDICE) in the University Hospital Medical Information Network (UMIN). The ethical committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences 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 J-RBR is registered to the Clinical Trial Registry of UMIN (registered number UMIN000000618) and is available in Japanese and English.

Clinical or renal histopathological diagnosis and laboratory data

Three classifications, clinical diagnosis, histological diagnosis by pathogenesis, and histological diagnosis by histopathology, were selected for each case (Supplementary Table) from the J-RBR. The classification of clinical diagnoses was determined as follows: acute nephritic syndrome, rapidly progressive nephritic syndrome, recurrent or persistent hematuria, chronic nephritic syndrome, nephrotic syndrome, renal disorder with metabolic disease, renal disorder with collagen disease or vasculitis, hypertensive nephropathy, inherited renal disease, acute renal failure, drug-induced nephropathy, renal transplantation, and others. The definitions of the former five clinical diagnoses were based on the clinical syndromes and glomerular histopathology in the classification of glomerular diseases [11]. Acute nephritic syndrome was defined as a syndrome characterized by the abrupt onset of hematuria, proteinuria, hypertension, decreased glomerular filtration, and edema. Rapidly progressive nephritic syndrome was defined as an abrupt or insidious onset of hematuria, proteinuria, anemia, and rapidly progressing renal failure. Recurrent or persistent hematuria included the insidious or abrupt onset of gross or microscopic hematuria with little or no proteinuria and no evidence of other features of nephritic syndrome. Chronic nephritic syndrome was defined as slowly developing renal failure accompanied by proteinuria, hematuria, with or without hypertension. Nephrotic syndrome was defined as massive proteinuria >3.5 g/day and hypoalbuminemia of <3 g/dL of serum albumin with or without edema or hypercholesteremia.

The renal histological diagnosis is classified either according to pathogenesis (A) or by histopathology (B) as follows: (A) primary glomerular disease (except IgAN), IgAN, purpura nephritis, lupus nephritis, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-positive nephritis, protein 3 (PR3)-ANCA-positive nephritis, anti-glomerular basement membrane antibody nephritis, hypertensive nephrosclerosis, thrombotic microangiopathy, diabetic nephropathy, amyloid nephropathy, Alport syndrome, thin basement membrane disease, infection-related nephropathy, transplanted kidney, and others; (B) minor glomerular abnormalities, focal and segmental glomerulosclerosis (FSGS), MN, mesangial proliferative glomerulonephritis, endocapillary proliferative glomerulonephritis, membranoproliferative glomerulonephritis (MPGN) (type I, III), dense deposit disease, crescentic and necrotizing glomerulonephritis, sclerosing glomerulonephritis, nephrosclerosis, acute interstitial nephritis, chronic interstitial nephritis, acute tubular necrosis, transplanted kidney, and others. IgAN (Berger disease) was separated from primary glomerular diseases on the basis of basic glomerular alterations in the classification of glomerular diseases [11]. Clinical data, including urinalysis, daily proteinuria, serum creatinine concentrations, total protein, albumin, and total cholesterol values were also recorded, but only the frequency of the disease is described here.

Statistics

Data were expressed as mean ± SD as appropriate. Statistical analyses were performed using the JMP software program, version 8 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of registered biopsies

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

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Table 1 Number of participating renal centers and registered renal biopsies on the Japan Renal Biopsy Registry (J-RBR) in 2007 and 2008

Year	2007	2008	Total
Renal centers	18	23	23
Total biopsies	818	1582	2400
Average age (y)	44.6 ± 20.7	44.2 ± 21.1	44.4 ± 21.0
Male	430	851	1281
Female	388	731	1119
Native kidneys	726	1400	2126
Average age (y)	45.2 ± 21.4	44.8 ± 22.0	44.9 ± 21.5
Male	378	751	1129
Female	348	649	997
Renal grafts	92	182	274
Average age (y)	40.5 ± 13.5	39.4 ± 16.3	39.8 ± 15.4
Male	52	100	152
Female	40	82	122

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 (Table 1). The average age of the patients was 44.6 ± 20.7 years of age in 2007 and 44.2 ± 21.1 years of age in 2008. A higher number of male patients than female patients were registered in both years (male patients 52.6% in 2007 and 53.8% in 2008). The distribution of the total number of renal biopsies according to age and gender are presented in Fig. 1, and reveals a different age and gender distribution in native kidneys and renal grafts.

The frequency of clinical diagnoses

The clinical diagnosis and renal histological diagnosis as classified by pathogenesis and by histopathology were determined for each biopsy. A clinical diagnosis of chronic nephritic syndrome was the most frequent, followed by nephrotic syndrome and renal transplantation in 2007, which was similar in 2008 (Table 2). In native kidneys, the majority of the cases corresponded to chronic nephritic syndrome, followed by nephrotic syndrome and recurrent or persistent hematuria or renal disorder with collagen disease or vasculitis in 2007 (Table 2). Similar frequencies of chronic nephritic syndrome, nephrotic syndrome and renal disorder with collagen disease or vasculitis were observed in 2008 (Table 2).

The frequency of pathological diagnoses

Pathological diagnoses were classified by pathogenesis (Table 3) and histopathology (Table 4). In the classification of pathogenesis, IgAN was diagnosed most frequently, followed by primary glomerular disease (except IgAN) and renal grafts both in 2007 and 2008 (Table 3). In the present cohort, except for renal grafts, the frequency of IgAN was 32.9%, followed by primary glomerular disease (except IgAN) (26.3%) and diabetic nephropathy (5.9%) in 2007 (Table 3). A slightly lower frequency of IgAN was present (30.2%), but similar frequencies of primary glomerular disease (except IgAN) (26.3%) and diabetic nephropathy (5.1%) were observed in 2008 (Table 3).

In the pathological diagnoses as classified by histopathology, mesangial proliferative glomerulonephritis was primarily observed in 2007 and 2008 (Table 4). In the present cohort, except for renal grafts, the frequency of mesangial proliferative glomerulonephritis was the highest followed by MN, minor glomerular abnormalities, nephrosclerosis, and crescentic and necrotizing glomerulonephritis in 2007 (Table 4). In 2008, mesangial proliferative glomerulonephritis was the most frequently diagnosed,

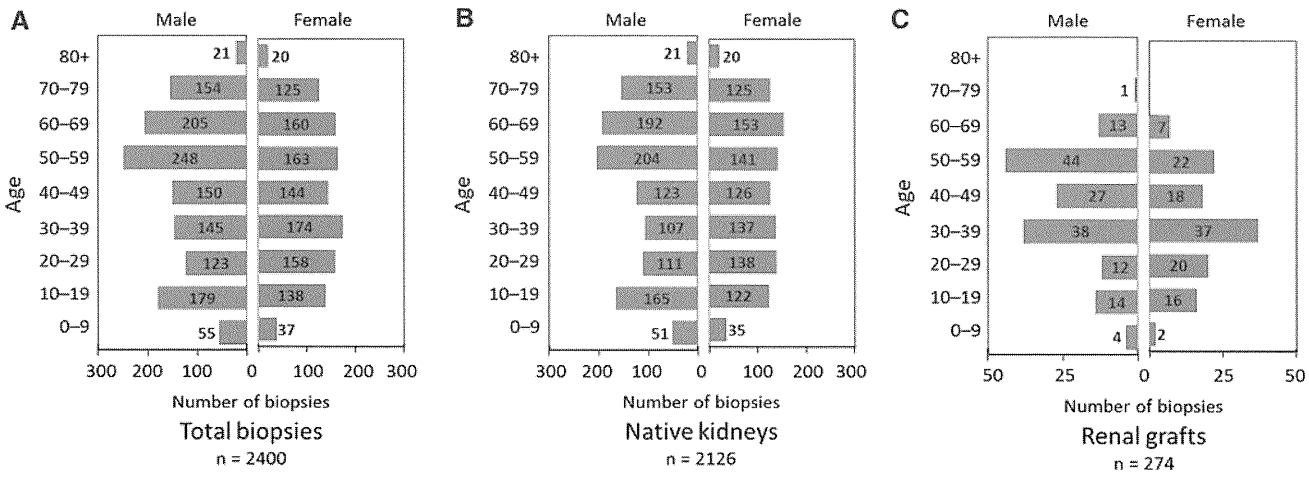

Fig. 1 Distribution of age ranges and gender in total renal biopsies (**a**), native kidneys (**b**), and renal grafts (**c**) in the combined data of 2007 and 2008

Table 2 Frequency of classification of clinical diagnoses

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	388	47.4	768	48.5	1156	48.2
Nephrotic syndrome	138	16.9	259	16.4	397	16.5
Renal transplantation	92	11.2	182	11.5	274	11.4
Renal disorder with collagen disease or vasculitis	41	5.0	87	5.5	128	5.3
Rapidly progressive nephritic syndrome	33	4.0	80	5.1	113	4.7
Recurrent or persistent hematuria	41	5.0	33	2.1	74	3.1
Renal disorder with metabolic syndrome	29	3.5	46	2.9	75	3.1
Hypertensive nephropathy	14	1.7	30	1.9	44	1.8
Acute nephritic syndrome	15	1.8	20	1.3	35	1.5
Acute renal failure	7	0.9	13	0.8	20	0.8
Drug-induced nephropathy	3	0.4	11	0.7	14	0.6
Inherited renal disease	5	0.6	8	0.5	13	0.5
Others	12	1.6	45	2.8	57	2.4
Total	818	100.0	1582	100.0	2400	100.0

Table 3 Frequency of pathological diagnoses as classified by pathogenesis

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
IgA nephropathy	239	29.2	424	26.8	663	27.6
Primary glomerular disease (except IgA nephropathy)	191	23.3	369	23.3	560	23.3
Renal graft	93	11.3	179	11.3	272	11.3
Diabetic nephropathy	43	5.2	71	4.5	114	4.8
Hypertensive nephrosclerosis	31	3.7	61	3.9	92	3.8
Lupus nephritis	29	3.5	59	3.7	88	3.7
MPO-ANCA-positive nephritis	25	3.0	58	3.7	83	3.5
Purpura nephritis	18	2.2	39	2.5	57	2.4
Amyloid nephropathy	12	1.4	22	1.4	34	1.4
Infection-related nephropathy	16	1.9	16	1.0	32	1.3
Thin basement membrane disease	11	1.3	5	0.3	16	0.7
Alport syndrome	1	0.1	9	0.6	10	0.4
PR3-ANCA-positive nephritis	1	0.1	7	0.4	8	0.3
Thrombotic microangiopathy	3	0.3	2	0.1	5	0.2
Anti-glomerular basement membrane antibody-type nephritis	0	0.0	4	0.3	4	0.2
Others	105	12.8	257	16.2	362	15.1
Total	818	100.0	1582	100.0	2400	100.0

with minor glomerular abnormalities being the second, and MN being the third (Table 4).

Primary glomerular disease (except IgAN) and nephrotic syndrome

In the cohort of primary glomerular disease as classified by pathogenesis, MN was predominant, followed by mesangial proliferative glomerulonephritis, minor glomerular abnormalities, and FSGS in 2007 (Table 5). In 2008, MN was still the most frequently diagnosed, present at the same frequency as minor glomerular abnormalities (Table 5).

In nephrotic syndrome as classified by clinical diagnosis, primary glomerular disease (except IgAN) was predominant, followed by diabetic nephropathy, amyloid nephropathy, IgAN, and lupus nephritis in 2007 (Table 6). A similar ordering of the disease frequencies was noted in 2008 (Table 6). Among the primary glomerular diseases

Table 4 Frequency of pathological diagnoses as classified by histopathology

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Mesangial proliferative glomerulonephritis	326	39.8	607	38.4	933	38.9
Renal graft	90	11.0	171	10.8	261	10.9
Membranous nephropathy	74	9.0	128	8.1	202	8.4
Minor glomerular abnormalities	52	6.3	143	9.0	195	8.1
Crescentic and necrotizing glomerulonephritis	32	3.9	87	5.5	119	5.0
Nephrosclerosis	38	4.6	77	4.9	115	4.8
Focal segmental glomerulosclerosis	32	3.9	65	4.1	97	4.0
Membranoproliferative glomerulonephritis (type I and III)	20	2.4	32	2.0	52	2.2
Chronic interstitial nephritis	24	2.9	21	1.3	45	1.9
Endocapillary proliferative glomerulonephritis	18	2.2	27	1.7	45	1.9
Sclerosing glomerulonephritis	10	1.2	33	2.1	43	1.8
Acute interstitial nephritis	7	0.9	18	1.1	25	1.0
Acute tubular necrosis	5	0.6	6	0.4	11	0.5
Dense deposit disease	1	0.1	5	0.3	6	0.3
Others	89	10.8	162	10.2	251	10.5
Total	818	100.0	1582	100.0	2400	100.0

Table 5 Frequency of pathological diagnoses as classified by histopathology in primary glomerular disease (except IgA nephropathy)

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Membranous nephropathy	60	31.4	95	25.7	155	27.7
Minor glomerular abnormalities	33	17.3	95	25.7	128	22.9
Mesangial proliferative glomerulonephritis	45	23.6	82	22.2	127	22.7
Focal segmental glomerulosclerosis	24	12.6	53	14.4	77	13.8
Membranoproliferative glomerulonephritis (type I and III)	13	6.8	19	5.1	32	5.7
Crescentic and necrotizing glomerulonephritis	5	2.6	6	1.6	11	2.0
Endocapillary proliferative glomerulonephritis	1	0.5	6	1.6	7	1.3
Nephrosclerosis	2	1.0	4	1.1	6	1.1
Dense deposit disease	1	0.5	3	0.8	4	0.7
Sclerosing glomerulonephritis	2	1.0	1	0.3	3	0.5
Others	5	2.6	5	1.4	10	1.8
Total	191	100.0	369	100.0	560	100.0

(except IgAN) in nephrotic syndrome, MN was dominant followed by minor glomerular abnormalities, such as minimal change nephrotic syndrome (MCNS), FSGS, and MPGN (type I and III) in 2007 (Table 7). In 2008, the frequency of minor glomerular abnormalities was predominant, followed by MN (Table 7).

Clinical diagnosis of MN, minor glomerular abnormalities, and FSGS

Subanalyses of subjects with a clinical diagnosis of MN, minor glomerular abnormalities, and FSGS were performed since these were the most common forms of primary glomerular diseases (except IgAN) (Tables 8, 9, 10). Nephrotic syndrome was the most common clinical diagnosis in MN and minor glomerular abnormalities (Tables 8, 9), whereas chronic nephritic syndrome was the most common in FSGS (Table 10). In the pathogenesis of minor glomerular abnormalities (total 195 cases), primary glomerular diseases (except IgAN) comprised 65.6% (128 cases), followed by others 13.8% (27 cases), IgAN 8.2% (16 cases) and thin basement membrane disease 5.1% (10 cases). In the pathogenesis of FSGS (total 97 cases), primary glomerular diseases (except IgAN) comprised 79.4%

Table 6 Frequency of pathological diagnoses as classified by pathogenesis in nephrotic syndrome

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Primary glomerular disease (except IgA nephropathy)	91	65.9	179	69.1	270	68.0
Diabetic nephropathy	15	10.9	15	5.8	30	7.6
Amyloid nephropathy	9	6.5	13	5.0	22	5.5
IgA nephropathy	8	5.8	9	3.5	17	4.3
Lupus nephritis	4	2.9	8	3.1	12	3.0
Purpura nephritis	1	0.7	4	1.5	5	1.3
Infection-related nephropathy	3	2.2	1	0.4	4	1.0
Thrombotic microangiopathy	1	0.7	0	0.0	1	0.3
MPO-ANCA-positive nephritis	0	0.0	1	0.4	1	0.3
Hypertensive nephrosclerosis	0	0.0	1	0.4	1	0.3
Others	6	4.3	28	10.8	34	8.6
Total	138	100.0	259	100.0	397	100.0

Table 7 Frequency of pathological diagnoses as classified by histopathology in primary glomerular disease (except IgA nephropathy) in nephrotic syndrome

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Minor glomerular abnormalities	29	31.9	79	44.1	108	40.0
Membranous nephropathy	40	44.0	56	31.3	96	35.6
Focal segmental glomerulosclerosis	10	11.0	25	14.0	35	13.0
Membranoproliferative glomerulonephritis (type I and III)	7	7.7	13	7.3	20	7.4
Mesangial proliferative glomerulonephritis	1	1.1	4	2.2	5	1.9
Crescentic and necrotizing glomerulonephritis	2	2.2	1	0.6	3	1.1
Endocapillary proliferative glomerulonephritis	1	1.1	0	0.0	1	0.4
Others	1	1.1	1	0.6	2	0.7
Total	91	100.0	179	100.0	270	100.0

Table 8 Frequency of clinical diagnoses in membranous nephropathy

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Nephrotic syndrome	44	59.5	66	51.6	110	54.5
Chronic nephritic syndrome	20	27.0	47	36.7	67	33.2
Renal disorder with collagen disease or vasculitis	7	9.5	9	7.0	16	7.9
Renal disorder with metabolic syndrome	1	1.4	1	0.8	2	1.0
Recurrent or persistent hematuria	1	1.4	0	0.0	1	0.5
Renal transplantation	0	0.0	1	0.8	1	0.5
Rapidly progressive nephritic syndrome	0	0.0	1	0.8	1	0.5
Acute nephritic syndrome	0	0.0	1	0.8	1	0.5
Drug-induced nephropathy	0	0.0	1	0.8	1	0.5
Others	1	1.4	1	0.8	2	1.0
Total	74	100.0	128	100.0	202	100.0

Table 9 Frequency of clinical diagnoses in minor glomerular abnormalities

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Nephrotic syndrome	29	55.8	82	57.3	111	56.9
Chronic nephritic syndrome	9	17.3	43	30.0	52	26.7
Recurrent or persistent hematuria	6	11.5	10	7.0	16	8.2
Renal disorder with collagen disease or vasculitis	1	1.9	5	3.5	6	3.1
Rapidly progressive nephritic syndrome	1	1.9	0	0.0	1	0.5
Renal disorder with metabolic syndrome	1	1.9	0	0.0	1	0.5
Acute nephritic syndrome	1	1.9	0	0.0	1	0.5
Drug-induced nephropathy	1	1.9	0	0.0	1	0.5
Inherited renal disease	0	0.0	1	0.7	1	0.5
Others	3	5.8	2	1.4	5	2.6
Total	52	100.0	143	100.0	195	100.0

Table 10 Frequency of clinical diagnoses in focal segmental glomerulosclerosis

Classification	2007		2008		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	18	56.3	32	49.2	50	51.5
Nephrotic syndrome	10	31.3	26	40.0	36	37.1
Inherited renal disease	2	6.3	0	0.0	2	2.1
Renal disorder with collagen disease or vasculitis	1	3.1	1	1.5	2	2.1
Rapidly progressive nephritic syndrome	1	3.1	1	1.5	2	2.1
Renal transplantation	0	0.0	1	1.5	1	1.0
Recurrent or persistent hematuria	0	0.0	1	1.5	1	1.0
Renal disorder with metabolic syndrome	0	0.0	1	1.5	1	1.0
Others	0	0.0	2	3.1	2	2.1
Total	32	100.0	65	100.0	97	100.0

Table 11 Profile of IgA nephropathy

IgA nephropathy	2007	2008	Total
Total native kidney biopsies (*n*)	239	421	660
Average age (y)	36.5 ± 19.0	36.4 ± 18.2	36.4 ± 18.5
Male (*n*)	112 (46.9%)[a]	219 (52.0%)[a]	331 (50.2%)[a]
Average age (y)	37.1 ± 18.9[b]	37.2 ± 19.3[b]	37.2 ± 19.1[b]
Female (*n*)	127 (53.1%)	202 (48.0%)	329 (49.8%)
Average age (y)	36.1 ± 19.2	35.4 ± 17.0	35.7 ± 17.8

[a] Ratio indicates percentage of each gender in each biopsy category

[b] Not significant as compared to another gender

(77 cases), followed by others 11.3% (11 cases) and hypertensive nephrosclerosis 4.1% (4 cases).

Subanalysis of IgAN

The profile, classification of clinical diagnosis, and the pathological diagnosis of IgAN, the most frequent glomerulonephritis on the J-RBR, were further analyzed (Tables 11, 12, 13). The percentage of IgAN detected in total biopsies and native kidneys was 27.5 and 31.0% in 2007 and 2008, respectively. The average age was the fourth decade in both genders. There was no difference in the proportion based on gender (Table 11). The majority of the clinical and pathological diagnoses were chronic

Table 12 Frequency of classification of clinical diagnoses in IgA nephropathy

Clinical diagnosis	2007		2008		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	197	82.4	387	91.9	584	88.5
Recurrent or persistent hematuria	23	9.6	17	4.0	40	6.1
Nephrotic syndrome	8	3.3	9	2.1	17	2.6
Rapidly progressive nephritic syndrome	8	3.3	1	0.2	9	1.4
Acute nephritic syndrome	2	0.8	4	0.9	6	0.9
Hypertensive nephropathy	0	0.0	2	0.5	2	0.3
Renal disorder with metabolic disease	1	0.4	0	0.0	1	0.2
Acute renal failure	0	0.0	1	0.2	1	0.2
Total	239	100.0	421	100.0	660	100.0

nephritic syndrome (Table 12) and mesangial proliferative glomerulonephritis (Table 13), respectively.

Other diseases

Rare diseases such as Alport syndrome, Fabry disease, lipoprotein glomerulopathy, and dense deposit disease (one case each) were registered in 2007, and one subject was diagnosed with POEMS syndrome in 2008.

Discussion

The J-RBR obtained data from 818 and 1582 patients with kidney disease and renal transplantation who submitted renal biopsies in 2007 and 2008, respectively. The main objectives of the registry were, based on the histopathological findings, to establish the frequency of glomerulopathies, tubulointerstitial diseases, renal vascular disorders, and renal grafts in renal biopsies in Japan. Data for all patients with histopathological evidence of renal disease at the participating centers were collected on standard forms and registered on the J-RBR program in the UMIN-INDICE. Chronic nephritic syndrome was the most frequent clinical diagnosis in both years of the registry. IgAN was the most frequently diagnosed disease in renal biopsies in 2007 and 2008, consistent with previous reports [8]. In patients with nephrotic syndrome, primary glomerular diseases (except IgAN) were predominant in both years.

Regarding the classification of clinical diagnosis in native kidney biopsies, more than half were diagnosed with chronic nephritic syndrome, which was usually accompanied by urinary abnormalities, as shown in Table 2. The frequency of clinical diagnosis may reflect the prevalence of renal biopsy in Japan. Indications of renal biopsy in Japan included urinary abnormalities such as mild-to-moderate proteinuria with or without hematuria, massive proteinuria such as nephrotic syndrome, rapidly progressive glomerulonephritis, and renal allografts (a protocol or episode biopsy). Solitary hematuria may be indicated after urological examinations. In Japan, all students in primary and junior high schools routinely undergo an annual urinalysis by the dip-stick test as one of the national health programs. Therafter students in high schools and universities and employees of companies submit to a urinalysis as part of a nationwide screening program. This social system promotes the early referral to nephrologists and may thus influence the frequency of chronic nephritic syndrome according to the clinical diagnoses of the J-RBR.

In the present study, IgAN was the most frequently diagnosed by pathological findings, which is consistent with a previous report [8]. The frequency of IgAN was 32.9% in 2007 and 30.2% in 2008 in native kidneys of patients registered on the J-RBR, which was less than that in the previous nationwide survey [8]. IgAN is the most common biopsy-proven renal disease among primary glomerulopathies in Asia as described in reports from

Table 13 Frequency of pathological diagnoses as classified by histopathology

Pathological diagnosis by histopathology	2007		2008		Total	
	n	%	*n*	%	*n*	%
Mesangial proliferative glomerulonephritis	228	95.4	398	94.5	626	94.8
Minor glomerular abnormalities	0	0.0	16	3.8	16	2.4
Crescentic and necrotizing glomerulonephritis	2	0.8	3	0.7	5	0.8
Sclerosing glomerulonephritis	3	1.3	0	0.0	3	0.5
Nephrosclerosis	1	0.4	1	0.2	2	0.3
Membranous nephropathy	1	0.4	1	0.2	2	0.3
Membranoproliferative glomerulonephritis (type I and III)	1	0.4	0	0.0	1	0.2
Others	3	1.3	2	0.5	5	0.8
Total	239	100.0	421	100.0	660	100.0

Korea [12] and China [13]. In the United States, IgAN is the most common primary glomerulopathy in young adult Caucasians and the most common cause of end-stage renal disease, while it was found to be rare in African Americans in whom FSGS remained more common [14]. In Australia, IgAN, FSGS, lupus nephritis, and vasculitis are the most common renal diseases in adults with a male predominance, excepting lupus nephritis [6]. In Europe, IgAN is the most frequent primary glomerulonephritis in several countries [2, 4, 5, 15], while MN is the most frequent in Macedonia [16], MPGN in Romania [17], and non-IgA mesangial proliferative glomerulonephritis in Serbia [18]. FSGS is the most frequent renal disease in a recent report from Brazil [19]. Because there is a different policy of renal biopsy practice in each country, it may not be easy to compare the different databases across countries. Instead, the changing frequency patterns of renal disease in the same country over a certain time period are useful to treat disease and reduce chronic kidney disease burden [20].

The frequency of nephrotic syndrome was 19.0% in 2007 and 18.5% in 2008 for patients registered on the J-RBR. Primary renal diseases were present in approximately two-thirds of all patients with nephrotic syndrome. MN was the most common primary nephrotic syndrome in 2007 (44.0%) and MCNS was the most common in 2008 (44.1%). The reason for this difference may depend on the cohort of registered biopsies in both years, since the number of patients registered was not as large as other registries [2, 4, 13, 19].

For the registry of patients with end-stage renal disease in Japan, 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 [21]. The combined data of the J-RBR with this dialysis registry will allow us to evaluate the long-term outcome of patients with various renal diseases in the near future. Similarly, the combined renal transplant registry data allows the evaluation of patient outcome. A sizeable frequency of renal grafts was registered on the J-RBR. Consequently, the future analysis of renal grafts, including the frequency of the protocol and episode biopsies and the precise histological diagnosis, will be necessary.

There is no overall registry of renal biopsies in Japan at the moment. It is noteworthy that the J-RBR is web-based, and a prospective registry system that can easily increase the number of participating centers and enlarge the number of patients enroled in the future. We cannot conclude that the present sample of patients on the J-RBR in 2007 and in 2008 is actually representative of the nationwide frequency of glomerular, tubulointerstitial, or renal vascular diseases or renal grafts in Japan. However, in the near future, 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 by utilizing the J-RBR system.

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Appendix

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Specific collaboration between rat membrane complement regulators Crry and CD59 protects peritoneum from damage by autologous complement activation

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Abstract

Background. The peritoneal cavity is isolated from the outside and is usually a sterile environment. Patients on peritoneal dialysis (PD) have PD fluid (PDF) infused into the peritoneal cavity. We previously showed that unregulated complement activation could contribute to the development of peritoneal inflammation in yeast peritonitis in PD therapy. In that situation, suppression of local complement activation is essential to protect the host from further injury. The membrane complement regulators (CRegs), Crry, CD55 and CD59, are expressed in the rat peritoneum, especially along the mesothelial cell layer.

Methods. We investigated CRegs' functional roles in the peritoneal cavity using blocking mAb against each CReg and complement activation in different PDFs.

Results. Blockade of any single CReg did not cause spontaneous peritoneal injury in rat. Combined blockade of Crry and CD59 induced focal peritoneal tissue injury and heavy accumulation of inflammatory cells with peritoneal edema at 24 h. Deposits of C3 and C5b-9 were found on the peritoneal surface after combined blocking of Crry and CD59. Systemic complement depletion by cobra venom factor abrogated these inflammatory changes. When combined blockade of Crry and CD59 was performed with PDF of different pH and glucose concentration in rats, the peritoneal injuries were enhanced with lower pH and higher glucose concentration. These results were confirmed by *in vitro* experiments using primary rat mesothelial cell culture.

Conclusions. Rat CRegs, Crry and CD59, specifically collaborate to control complement activation in rat peritoneum. During PD, impairment of CReg might contribute to the development of severe peritoneal inflammation.

Keywords: complement; immunology; peritoneal dialysis; peritoneal membrane

Introduction

Complement (C) activation play important roles in innate immunity, protecting the host from invading microorganisms and tumor cells. However, uncontrolled activation of C is harmful for the host. C regulators (CRegs) play important roles to control C activation in the host in both the fluid phase in plasma and solid phase on the cell membrane [1]. Membrane CRegs exist on the membranes to protect self tissues. In animal experiments, including our reports, neutralization of CRegs acting at the C3 convertase level exacerbated various pathologies [2–4]. In most tissues, single neutralization of CD59, a membrane attack complex (MAC; C5b-9) regulator, did not cause significant pathologic changes. An exception was the joint, where neutralization of CD59 induced synovial inflammation [5]. We have shown that inflammation was enhanced in joint and kidney when rat CRegs Crry and CD59 were simultaneously blocked at these sites [6,7].

It is known that some physiological states, such as acidosis, induce C activation [8]. Exposure of the peritoneum to peritoneal dialysis (PD) fluid (PDF) commonly causes physical stresses, including hypertonic and acidic stress [9,10]. In pathogenic conditions such as peritonitis in PD patients, increased C activation products were detected in serum, while C activation products were observed in the peritoneal cavity in chronic PD patients [11–14]. *In vitro*, exposure of human peritoneal mesothelial cells to PDF caused up-regulation in production of C3 and C4, suggesting that local C production in peritoneum might be asso-

Table 1. *In vivo* experimental protocol

Group	Number of rats (*n*)	Pretreatment	Injected mAbs (mg/each rat) 5I2	RDIII7	6D1	Timing of the observation (hours)
1	4, 6, 4	None	0	0	0	6, 24, 72
2	6	None	0.5	0	0	24
3	6	None	0	0.5	0	24
4	6	None	0	0	0.5	24
5	6	None	0.5	0.5	0	24
6	6	None	0	0.5	0.5	24
7	4, 6, 4	None	0.5	0	0.5	6, 24, 72
8	6	CVF	0.5	0	0.5	24
9	6	Vehicle	0.5	0	0.5	24

ciated with host defense and inflammation [12]. It was also reported that mannose-binding lectin, the key component of the lectin pathway, was lower in sera of chronic PD plasma, perhaps causing increased infection susceptibility [15]. However, there is still very little information regarding peritoneal C activation in PD patients exposed to PDF.

Information on peritoneal expression of CReg is limited. CD59, a CReg inhibiting at MAC level, was expressed on mesothelium in human peritoneum [16]. In rats, we previously described expression of Crry, CD55 and CD59, but not CD46 [17], and we showed that decreased CReg expression contributed to the development of peritonitis [18]. However, there are no reports describing the functional roles of CReg in normal peritoneum. Here, we investigated roles of CRegs using combinations of mAbs to neutralize function of single or multiple CReg in rat peritoneum, particularly in the context of exposure to PDF.

Materials and methods

Animals

Male Sprague-Dawley (SD) rats weighing ~250 g (Chubu Kagaku Shizai; Nagoya, Japan) were used. All animal experiments were carried out accord-

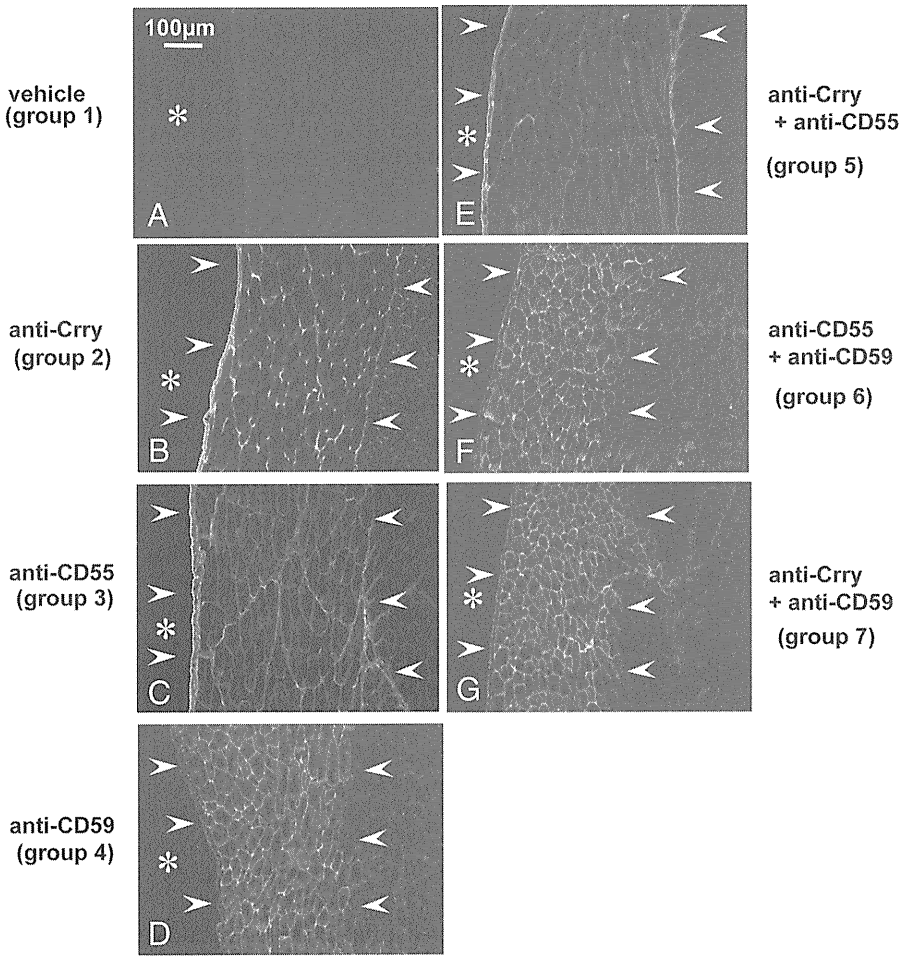

Fig. 1. Binding of anti-CRegs in peritoneum after 24 h. Typical patterns of binding of anti-Crry (Group 2; frame **B**), anti-CD55 (Group 3; frame **C**) or anti-CD59 (Group 4; frame **D**) at 24 h post-injection. Combination of two anti-CRegs, selected from anti-Crry, anti-CD55 and anti-CD59, was also administered; the binding of mAbs is shown in frames **E** (Crry/CD55; Group 5), **F** (CD55/CD59; Group 6) and **G** (Crry/CD59; Group 7). Frame **A** is a negative control injected with vehicle only. The peritoneal surface was labeled as '*'. Arrowheads show the IgG binding. Original magnification is ×200. The scale of specimens is shown in the left-upper corner of frame A.

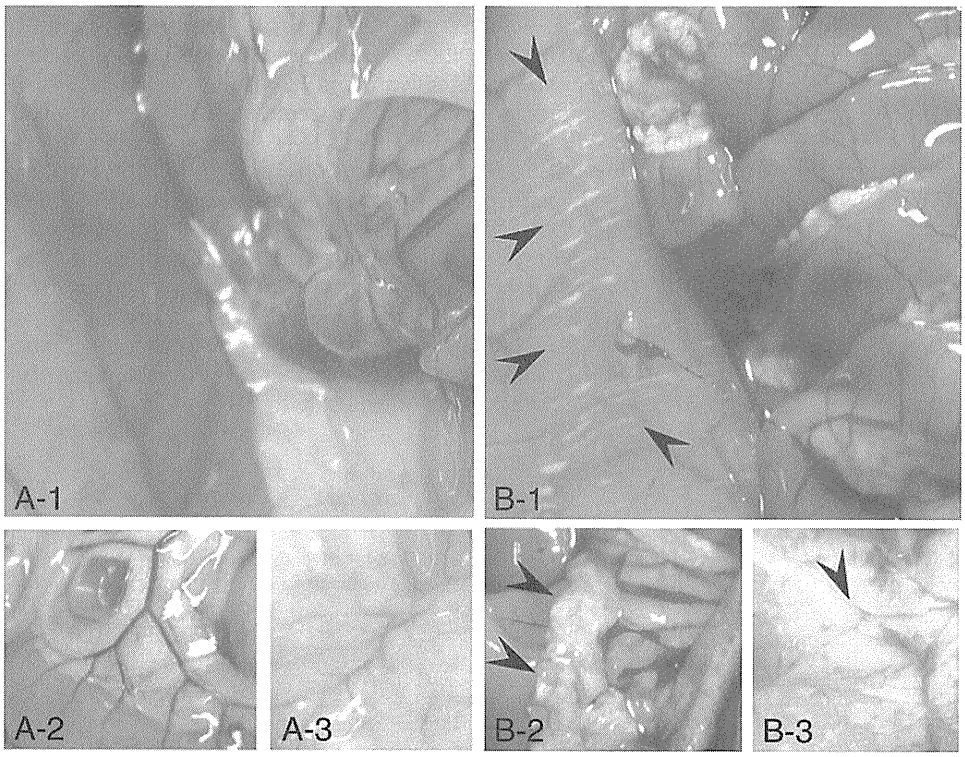

Fig. 2. Macroscopic changes in peritoneum at 24 h. For all experimental groups except Group 7, there were no significant macroscopic changes in the peritoneum; the left photo set shows peritoneum from rats treated with anti-Crry + anti-CD55 (Group 5) as an example (**A-1**, **A-2** and **A-3**). The right photo set shows macroscopic appearance in rats treated with anti-Crry + anti-CD59 (Group 7; **B-1**, **B-2** and **B-3**). White stripes are seen on parietal peritoneum (arrowheads in frame B-1), white granules in mesenteric vessels (arrowheads in frame B-2) and fibrous changes in retroperitoneum (arrowhead in frame B-3). Frames A-2 and B-2 show vessels in visceral peritoneum. Frames A-3 and B-3 are retroperitoneum.

ing to the Animal Experimentation Guide of Nagoya University School of Medicine.

Reagents and antibodies

Mouse mAbs against rat CRegs Crry (mAb 5I2), CD46 (MM.1), CD55 (RDIII-7) and CD59 (6D1) were characterized as described [17,19–21]. All mAbs were mouse mAbs of isotype IgG1; all except MM.1 were known to block the function of the respective CReg. FITC-labeled rabbit anti-mouse IgG was purchased from Cappel Labs (Westchester, PA) and was absorbed with normal rat serum (RS). Cobra venom factor (CVF) was purified from lyophilized cobra venom *Naja naja* (Sigma-Aldrich, St. Louis, MO) and was administered as described [5]. Systemic C depletion was confirmed by measuring C hemolytic activity [5].

Table 2. Summary of the results at 24 h after CReg neutralization

Group (*n*)	Macroscopic findings	Peritoneal effusion (mL)[a]	C3 deposition	C5b-9 deposition
1 (6)	−	0	±	−
2 (6)	−	0	±	−
3 (6)	−	0	±	−
4 (6)	−	0	±	−
5 (6)	−	0	±	−
6 (6)	−	0	±	−
7 (6)	+	6.8 ± 0.69	++	+
8 (6)	−	0	−	−
9 (6)	+	6.38 ± 3.13	++	+

[a]The data are displayed as mean ± SE.

Experimental protocol

Firstly, rats were intraperitoneally (i.p.) injected with 0.5 mg of mAb, either singly or in combinations according to Table 1. These mAbs were diluted in 10 mL of 4.25% PDF (Dianeal PD-4 4.25%^{TM}; pH ~5; Baxter, Tokyo, Japan; PD4 4.25%). After 24 h, rats were sacrificed and parietal peritoneum collected for examination. To confirm the requirement for C activation to develop peritonitis following blockade of Crry and CD59, systemic C inhibition was achieved using 25 units CVF in 0.5 mL isotonic saline intravenously 24 h before neutralization of CRegs.

Effects of neutralizing Crry and CD59 under different osmotic and pH conditions

In a separate experiment, we simultaneously neutralized two CRegs, Crry and CD59, using mAbs diluted in sterile PBS (isotonic, pH7.4), 1.5% (pH ~6) PDF (Dianeal-N PD-4 1.5%^{TM}; pH ~6; Baxter; NPD4 1.5%), 1.5% (pH ~5) PDF (Dianeal PD-4 1.5%^{TM}; pH ~5.0; Baxter; PD4 1.5%) or 4.25% (pH ~5) PDF (PD4 4.25%). After 24 h, rats were sacrificed and parietal peritoneum collected for examination.

Histological analysis

The parietal peritoneum was dissected in strips (four strips, ~5 × 30 mm, from each side of parietal peritoneum). Two strips from each side of the parietal peritoneum were randomly selected, fixed in 20% buffered formalin and embedded in paraffin. Sections of 4.5 μm thick were stained with hematoxylin and eosin for histological analysis. The other strips were used for immunohistochemical analysis. To estimate tissue damage in parietal peritoneum, 20 fields were randomly observed and scored at ×100 magni-

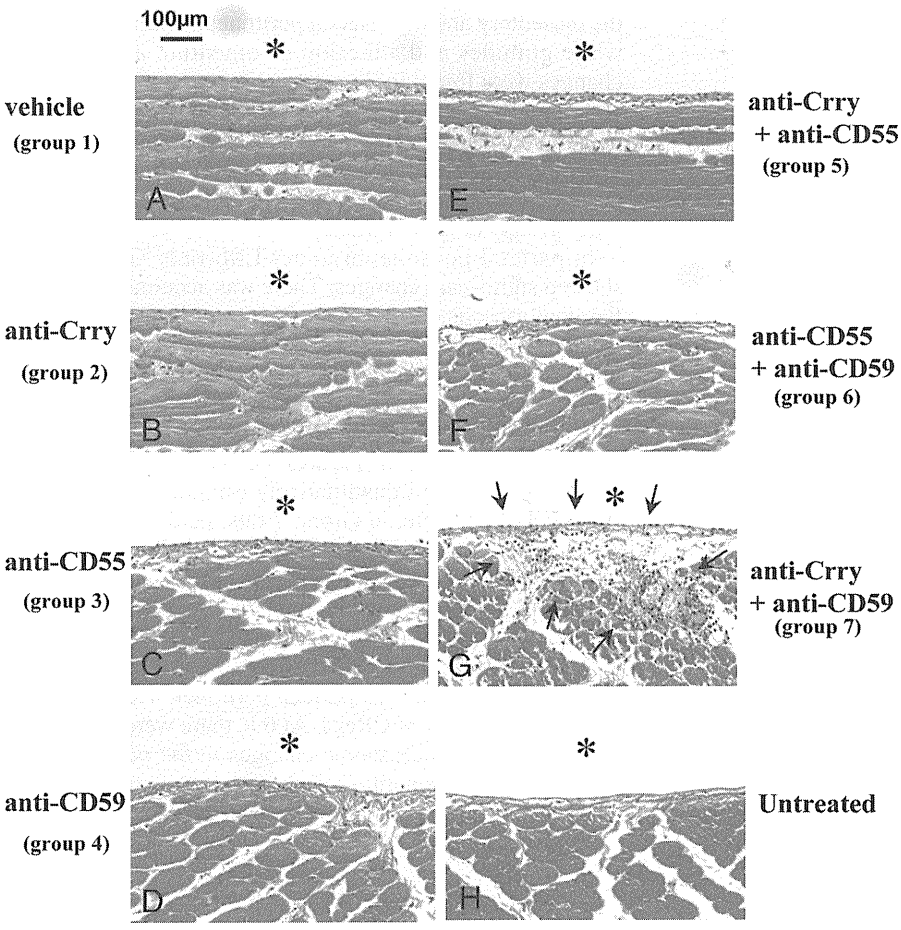

Fig. 3. Light microscopy changes in parietal peritoneum at 24 h after neutralization of CRegs. The mAb treatment administered is displayed to the left of each frame. Original magnification is ×200. Frames **A**, **B**, **C**, **D**, **E**, **F** and **G** show typical images from Groups 1 (vehicle), 2 (anti-Crry), 3 (anti-CD55), 4 (anti-CD59), 5 (anti-Crry + anti-CD55), 6 (anti-CD55 + anti-CD59) and 7 (anti-Crry + anti-CD59), respectively. Frame **H** shows peritoneum of untreated rat. The bar in the left-upper corner in frame A is shown as scale of 100 μm.

fication under light microscopy (LM). The severity of peritoneal damage in each rat was scored according to the following formula:

Severity of peritoneal damage (%) = [(total number of fields with peritoneal damage) / 20] × 100

Degree of peritoneal damages in each rat was estimated as follows: 0, 0% peritoneum damaged; 1, <25%; 2, 25–50%; 3, 50–75%; and 4, >75%.

Immunohistochemical analysis

Peritoneal strips obtained as above were snap-frozen, sections of 4.5 μm thick were prepared with a cryostat and fixed in acetone according to our previous report [18]. For the detection of infiltrating cells, frozen sections were incubated with FITC-labeled mouse anti-rat leukocyte common antigen (LCA) mAb (clone OX1; Chemicon International, Temecula, CA) or with FITC-labeled mouse anti-rat monocyte mAb (clone ED1; Serotec, Indianapolis, IL). To investigate C3 deposition, FITC-labeled polyclonal goat anti-rat C3 (Cappel, Solon, OH) was incubated on frozen sections. For the detection of MAC, frozen sections were incubated with rabbit anti-rat C9 followed by incubation with FITC-labeled goat anti-rabbit IgG (Cappel) absorbed with normal RS (1:1/v:v). For C3 and C9/MAC staining, normal rabbit serum was used as negative control for Ab and peritoneum of untreated rats was used as negative control tissue. To score deposition of C3 or C9/MAC, a semi-quantitative scale was used: (−) negative, (±) trace, (+) positive staining < 10% of total surface area and (++) positive staining area > 10%. The number of LCA-positive cells or ED-1 positive cells per field was calculated by counting positive cells in 20 sequential fields and taking the average.

Neutralization of CRegs in primary cell cultures of rat mesothelial cells

Primary cultures of rat mesothelial cells were obtained from SD rat omentum using a modification of a previous report [22,23] (Supplementary 1). Cells were plated at 2.0×10^5 cells/well in M199 medium with 10% FBS and incubated for 12 h. The cells were then incubated in M199 medium with RS or with heat-inactivated RS (incubated at 56°C for 30 min) for 1 h. Firstly, with the aim of studying the effect of neutralizing rat CRegs, preliminary experiments were performed to identify the concentration of RS required to induce 50% positive deposition of C3 in rat mesothelial cells. The concentration of RS was adjusted from 0 to 10%, and a dose of 2% RS or heat-inactivated RS was chosen for the following *in vitro* experiments. For *in vitro* neutralization of CRegs, 0.05 mg/mL of mAb 5I2, RDIII7 or 6D1, or every combination of two of them, with RS or heat-inactivated RS, was added to the medium and the mesothelial cells were incubated for 1 h at 37°C. To study the effects of pH or glucose concentration on the neutralizing of CRegs Crry and CD59 on rat mesothelium, we incubated mesothelial cells as described above but with 2% RS or heat-inactivated RS in pH 5.0, 5.4, 6.4 or 7.4 M199 medium adjusted by addition of HCl or in 0, 1.50, 2.5 or 4.25% glucose in M199 medium. After the incubation, the cells were washed with PBS three times and C3 deposition on the cells was detected with FITC-labeled anti-rat C3. Cells were double-stained by DAPI (Sigma-Aldrich) to facilitate cell counting. Total and C3-positive cells were counted in 20 fields randomly, and the C3 deposition was calculated by the following formula;

Degree of C3 deposition (%) = number of C3 positive cells / total number of cells × 100.

The above experiments were repeated five times.