Table 2 Comparison of GFR among screened subjects in Okinawa and Ibaraki: normal blood pressure and normal fasting plasma glucose

	Ibaraki	Okinawa	*P* value
Men			
40–49	76.5 (12.9), $N = 4{,}416$	77.9 (13.8), $N = 5{,}812$	<0.0001
50–59	74.4 (13.5), $N = 7{,}356$	74.9 (14.3), $N = 5{,}155$	NS
60–69	69.3 (13.6), $N = 12{,}093$	70.1 (14.2), $N = 4{,}364$	<0.01
70–79	65.7 (14.4), $N = 10{,}095$	66.7 (15.0), $N = 3{,}807$	<0.001
80 and over	61.4 (15.2), $N = 2{,}174$	61.2 (16.2), $N = 1{,}037$	NS
Women			
40–49	80.5 (15.3), $N = 15{,}428$	85.9 (16.1), $N = 8{,}765$	<0.0001
50–59	76.6 (15.0), $N = 24{,}392$	80.5 (16.1), $N = 8{,}921$	<0.0001
60–69	72.5 (15.0), $N = 24{,}103$	74.7 (15.1), $N = 7{,}419$	<0.0001
70–79	67.4 (14.9), $N = 13{,}801$	68.6 (15.5), $N = 5{,}946$	<0.0001
80 and over	61.9 (15.6), $N = 2{,}403$	62.1 (19.2), $N = 1{,}847$	NS

Table 3 Comparison of the prevalence of low GFR, <45 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 among screened subjects in Okinawa to those in Ibaraki (reference): total screened

	GFR <45	*P* value	GFR <60	*P* value
Men				
40–49	2.37	<0.01	0.93	NS
50–59	1.44	<0.01	1.42	<0.0001
60–69	1.10	NS	0.84	<0.0001
70–79	1.29	<0.0001	0.85	<0.0001
80 and over	1.50	<0.0001	1.06	<0.05
Total	1.04	NS	0.76	<0.0001
Women				
40–49	2.1	<0.05	0.65	<0.0001
50–59	2.34	<0.0001	1.40	<0.0001
60–69	0.86	NS	0.56	<0.0001
70–79	1.11	<0.05	0.76	<0.0001
80 and over	1.26	<0.0001	0.95	<0.05
Total	1.27	<0.0001	0.75	<0.0001

Table 4 Comparison of the prevalence of low GFR, <45 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 among screened subjects in Okinawa to those in Ibaraki (reference): normal blood pressure and normal fasting plasma glucose

	GFR < 45	*P* value	GFR < 60	*P* value
Men				
40–49	2.28	NS	0.86	<0.05
50–59	1.43	NS	1.47	<0.0001
60–69	1.08	NS	0.84	<0.0001
70–79	1.19	<0.05	0.84	<0.0001
80 and over	1.65	<0.0001	1.00	NS
Total	0.97	NS	0.73	<0.0001
Women				
40–49	2.72	<0.01	0.65	<0.0001
50–59	2.60	<0.0001	1.37	<0.0001
60–69	0.71	<0.01	0.53	<0.0001
70–79	1.01	NS	0.73	<0.0001
80 and over	1.14	NS	0.92	<0.05
Total	1.18	<0.001	0.72	<0.0001

enzymatic method to measure serum creatinine. The enzymatic method is more precise and accurate than the Jaffe method, which usually overestimates serum creatinine due to interference from the non-creatinine chromogen. Nevertheless, we further confirmed that the difference is still evident when using the original Japanese Society of Nephrology GFR estimation equation (S. Matsuo et al., personal observation).

The strengths of the present study were as follows: (1) eGFR was calculated using the serum creatinine value after calibration and standardization, (2) both cohorts were large enough to compare by age and sex, (3) CKD prevalence was also evaluated using the two equations currently available in Japan.

There were some limitations of the present study: (1) Serum creatinine was not measured at a single laboratory, although assay methods of the participating laboratories were evaluated by standard samples from the Cleveland Clinic and the inter-laboratory coefficient of variation was very small (0.88%), (2) The formula for estimating GFR was developed using CKD patients; therefore, it is not applicable to a healthy population. In particular, underestimation is possible in those with an eGFR of more than 60 ml/min/1.73 m^2 [6]. Serum creatinine concentration is affected not only by GFR, but by various other factors as well, such as muscle mass, sex, race, diet, drugs, and tubular function. Ideally, the clearance of exogenous GFR markers, such as inulin, should be measured for GFR estimation, but the method is time-consuming and difficult and is not feasible for community-based screening. The Kidney Disease Improving Global Outcomes (KDIGO) group has initiated an action to improve clinical practice by

introducing GFR estimating equations that were developed for a large cohort of a variety of racial and other groups for international comparisons [27–29]. Asian populations, including the Japanese, generally have low muscle mass and low protein intake, which could impair the performance of the MDRD study equation, (3) Clinical information, such as inflammation, nutritional status, or drug treatment, was not included in the registry data.

In conclusion, the findings of the present study revealed that there are significant regional differences in CKD prevalence among screened subjects in Japan. Although, our results may need to be confirmed in other parts of Japan. Reasons for the difference in CKD prevalence remain speculative. Generally, people in Okinawa are short in stature and have a larger body mass index. Lifestyle habits, such as smoking, drinking, and exercise among people in Okinawa also differ from those in Ibaraki. The observed differences in ESRD prevalence might be at least partly due to the difference in the CKD prevalence. Further studies on CKD progression and background demographics in the two cohorts are warranted.

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Conflict of interest statement We have no conflict of interest.

References

1. Nakai S, Wada A, Kitaoka T, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2004). Therap Apher Dial. 2006;10:476–97.
2. Kimura Y, Takishita S, Muratani H, et al. Demographic study of first-ever stroke and acute myocardial infarction in Okinawa, Japan. Intern Med. 1998;37:736–45.
3. Kurokawa K. Salt, kidney and hypertension: why and what to learn from genetic analyses? Nephron. 2001;89:369–76.
4. Tanaka H, Shiohira Y, Uezu Y, et al. Metabolic syndrome and chronic kidney disease in Okinawa, Japan. Kidney Int. 2006;69:369–74.
5. Tozawa M, Iseki C, Tokashiki K, et al. Metabolic syndrome and risk of developing chronic kidney disease in Japanese adults. Hypertens Res. 2007;30:937–43.
6. Imai E, Horio M, Nitta K, et al. Modification of the MDRD study equation in Japan. Am J Kidney Dis. 2007;50:927–37.
7. Imai E, Horio M, Nitta K, et al. Estimation of glomerular filtration rate by the MDRD equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11:41–50.
8. Imai E, Horio M, Iseki K, et al. Prevalence of chronic kidney disease (CKD) in Japanese general population predicted by MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11:156–63.
9. Iseki K, Iseki C, Ikemiya Y, et al. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49:800–5.
10. Iseki K. The Okinawa screening program. J Am Soc Nephrol. 2003;14(Suppl 2):S127–30.
11. Ishida K, Ishida H, Narita M, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
12. Irie F, Iso H, Sairenchi T, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int. 2006;69:1264–71.
13. Yamagata K, Ishida K, Sairenchi T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71:159–66.
14. Usami T, Koyama K, Takeuchi O, et al. Regional variations in the incidence of end-stage renal failure in Japan. JAMA. 2000;284:2622–4.
15. Usami T, Nakao N, Fukuda M, et al. Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan. Kidney Int. 2003;64:1445–9.
16. Furumatsu Y, Nagasawa Y, Hamano T, et al. Integrated therapies including erythropoietin decrease the incidence of dialysis: lessons from mapping the incidence of end-stage renal disease in Japan. Nephrol Dial Transplant. 2008;23:984–90.
17. Perkovic V, Cass A, Patel AA, et al. High prevalence of chronic kidney disease in Thailand. Kidney Int. 2008;73:473–9.
18. Coresh J, Byrd-Holt D, Astor B, et al. Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 –2000. J Am Soc Nephrol. 2005;16:180–8.
19. Zuo L, Ma YC, Zhou YH, et al. Application of GFR-estimating equations in Chinese patients with chronic kidney disease. Am J Kidney Dis. 2005;45:463–72.
20. Coresh J, Astor B, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41:1–12.
21. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. J Am Med Assoc. 2007;298:2038–47.
22. Iseki K. Chronic kidney disease in Japan. Int Med. 2008;47:681–9.
23. Vikse BE, Irgens LM, Leivestad T, et al. Low birth weight increases risk for end-stage renal disease. J Am Soc Nephrol. 2008;19:151–7.
24. Ritz E. Is the renal risk of adults determined in utero? Kidney Int. 2007;72:667–8.
25. Levey A, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–54.
26. Murthy K, Stevens L, Stark P, et al. Variation in the serum creatinine assay calibration: a practical application to glomerular filtration rate estimation. Kidney Int. 2005;68:1884–7.
27. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: Approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int. 2007;72:247–59.
28. Hallan S, Coresh J, Astor B, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006;17:2275–84.
29. Uhlig K, MacLeod A, Craig J, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease Improving Global Outcomes (KDIGO). Kidney Int. 2006;70:2058–65.

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ORIGINAL ARTICLE

Prevalence of anemia according to stage of chronic kidney disease in a large screening cohort of Japanese

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Abstract
Background The prevalence of chronic kidney disease (CKD) is high in developed countries, including Japan. However, little is known about the prevalence of anemia according to the estimated glomerular filtration rate (eGFR) among Japanese.
Methods We studied screenees on the Okinawa General Health Maintenance Association (OGHMA) registry in 1993 ($N = 94,602$; 54,848 women and 39,754 men) who had both serum creatinine and hematocrit data. Anemia was defined as follows: hematocrit level <40% in men, <32% in women aged <50 years, and <35% in women aged ≥50 years. GFR was estimated using a new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female).
Results The prevalence of anemia clearly increased as CKD progressed below an eGFR of 60 ml/min per 1.73 m^2 in both genders. Logistic analysis adjusted with body mass index and older age (≥70 years) revealed that the odds ratio for complications of anemia was significantly increased below an eGFR of 45 ml/min per 1.73 m^2 in women and 90 ml/min per 1.73 m^2 in men. The association of lower kidney function with anemia was found to be more prevalent: adjusted odds ratio ≥2.0, from approximately 50 ml/min per 1.73 m^2.
Conclusion The present study suggested that there might be as many as 1,000,000 people with CKD stage 3–5 complicated with anemia in Japan.

Keywords Chronic kidney disease · Anemia

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Introduction

Accumulating evidence has shown that even early-stage chronic kidney disease (CKD) is a risk factor for developing cardiovascular disease (CVD) [1–3]. In addition to traditional risk factors such as hypertension, anemia may be associated with CVD among general subjects [4]. Similarly, it has been reported that low hemoglobin, especially together with CKD, increases the risk of coronary heart disease (CHD), CHD-related death, and stroke [5–8]. Since anemia accelerates the progression of CKD and advanced CKD is likely to be complicated with anemia, the combination of anemia and CKD, which promote each other in a vicious circle, could result in an increased risk of CVD and vice versa, that is, cardio-renal anemia syndrome [9]. Therefore, it is critical to identify CKD patients complicated with anemia.

Recent studies have estimated that the incidence of mild kidney dysfunction is substantially high in the general population worldwide, though it varies across countries [10–13]. In the advanced stages of kidney failure, anemia is a common complication due to an inappropriately reduced endogenous erythropoietin production [14]. However, previous studies performed in the USA have found that even mild kidney dysfunction, with an estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2, had a

significant impact on the occurrence of anemia [15, 16]. The study by Astor et al. [16] also demonstrated that there was a significant racial difference in the relationship between kidney function and anemia, with Japanese reported to have a much higher prevalence of CKD than US subjects [12, 17]. However, it is not yet known whether Japanese have a much higher prevalence of CKD complicated with anemia.

In this study, we investigated the prevalence of anemia according to CKD stage in a large community-based screening of Japanese subjects.

Methods

About OGHMA

Screening program: The Okinawa General Health Maintenance Association (OGHMA), a nonprofit organization founded in 1972 and currently under the direction of Drs. Ikemiya and Kinjo, conducts a large community-based annual health examination. Once each year, the staff, doctors, and nurses visit residences and workplaces throughout the prefecture to carry out health examinations. All subjects participate voluntarily in the screening. The OGHMA personnel provide mass screening, inform the participants of their results, and when necessary, recommend further evaluation or treatment. This process includes an interview concerning health status, a physical examination, and urine and blood tests. A nurse or doctor measures blood pressure using a standard mercury sphygmomanometer with the subject in sitting position. Dipstick testing for proteinuria, hematuria, and glucosuria (Ames Dipstick, Tokyo, Japan) is performed in spontaneously voided fresh urine. Proteinuria is defined as a dipstick urinalysis score of 1+ or more. Body mass index (BMI) is calculated as weight (kg) divided by the square of height (m). Computer-based data were available from April 1, 1993 through March 31, 1994 (n = 143,948) for the 1993 screening.

Participants

For the purposes of the present study, we examined OGHMA 1993 screenees who had both serum creatinine (SCr) and hematocrit data (N = 94,602; 54,848 women and 39,754 men). SCr was measured using a modified Jaffe's reaction in an autoanalyzer at the OGHMA laboratory.

Assessment of kidney function

Kidney function was evaluated by eGFR, which was calculated using the new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female) [18]. For calculating eGFR, we applied the value of SCr in enzymatic methods, which was calculated by the following equation: SCr (enzyme) = (SCr (Jaffe) − 0.194)/1.079 [19].

Definition of anemia, clinical data, and analysis

Anemia was defined according to the Japanese Society for Dialysis Therapy (JSDT) guidelines and the kidney disease outcomes quality initiative (K/DOQI) guidelines, which take both age and sex into account: men, <40%; women aged <50 years, <32%; and women aged ≥50 years, <35% [20, 21]. Diabetes mellitus (DM) was diagnosed when fasting plasma glucose levels were >126 mg/dl. Subjects who were already on chronic dialysis were excluded from the screening registry. To analyze the effect of kidney function on the prevalence and risk of anemia, subjects were divided into following six groups: less than 15 ml/min per 1.73 m^2, from 15 to 29 ml/min per 1.73 m^2, from 30 to 44 ml/min per 1.73 m^2, from 45 to 59 ml/min per 1.73 m^2, from 60 to 90 ml/min per 1.73 m^2, and more than 90 ml/min per 1.73 m^2.

According to the recently published JSDT Guideline for Renal Anemia in Chronic Kidney Disease, anemia was defined as <35% in women [22]. We also analyzed using this definition in women.

Statistics

Statistical significance of differences in characteristics across participants was examined using the t test (continuous variables), and the Wald chi-square test (categorical variables) was carried out. We compared values of hematocrit and prevalence of anemia between the different levels of clinical variables such as BMI, age, and eGFR by Scheffé's multiple comparison methods after analysis of variance (ANOVA). Multiple logistic analysis was done to examine the correlates of anemia by variables such as eGFR category, sex, older age (>70 years), and BMI category. Data are expressed as mean (standard deviation, SD). A P value of less than 0.05 was considered statistically significant.

Results

OGHMA population

Of total of 143,948 OGHMA subjects, 94,602 (65.7%: 54,848 women and 39,754 men) had measurements of both SCr and hematocrit levels. The clinical characteristics of the screened subjects according to gender are summarized in

Table 1 Characteristics of screened subjects in 1993 in Okinawa, Japan

Variable	All (N = 94,602)	Men (N = 39,754)	Women (N = 54,848)	P value
Age (years)	54.7 ± 15.3	53.5 ± 15.7	55.6 ± 14.9	<0.0001
BMI (kg/m^2)	24.0 ± 3.4	24.1 ± 3.2	23.9 ± 3.5	<0.0001
SBP (mmHg)	127.4 ± 17.7	129.4 ± 16.8	126.0 ± 18.1	<0.0001
DBP (mmHg)	76.6 ± 10.5	78.6 ± 10.4	75.1 ± 10.3	<0.0001
Urine protein (%)	3504 (3.8)	1774 (4.5)	1730 (3.3)	<0.0001
Hematocrit (%)	41.4 ± 4.1	44.5 ± 3.3	39.2 ± 3.0	<0.0001
Estimated GFR (ml/min per 1.73 m^2)	79.3 ± 20.1	79.8 ± 18.6	78.9 ± 21.1	<0.0001
Anemia (%)	5450 (5.8)	3056 (7.7)	2399 (4.4)	<0.0001
Serum creatinine (mg/dl)	0.98 ± 0.21	1.10 ± 0.20	0.89 ± 0.17	<0.0001
Diabetes (FPG ≥ 126 mg/dl)	3103 (4.8)	1711 (6)	1392 (3.8)	<0.0001
Hypertension	28312 (30.0)	13309 (33.6)	15003 (27.4)	<0.0001
Age (years)				
20–29	5423 (5.7)	2773 (7.0)	2650 (4.8)	
30–39	11802 (12.5)	5746 (14.5)	6056 (11.0)	
40–49	17612 (18.6)	7723 (19.4)	9889 (18.0)	
50–59	19996 (21.1)	7684 (19.3)	12312 (22.4)	
60–69	22446 (23.7)	9035 (22.7)	13411 (24.5)	
≥70	17323 (18.3)	6793 (18.3)	10530 (19.2)	
Estimated GFR (ml/min per 1.73 m^2)				
≥90	25258 (26.7)	10709 (26.9)	14549 (26.5)	
60–89	54042 (57.1)	24100 (60.6)	29942 (54.1)	
45–59	13287 (14.0)	4360 (11.0)	8927 (16.3)	
30–44	1829 (1.9)	524 (1.3)	1305 (2.4)	
15–29	151 (0.2)	47 (0.1)	104 (0.2)	
<15	35 (0.04)	14 (0.04)	21 (0.04)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose

Table 1. The prevalence of subjects aged 60 years or older was approximately 40%, which included about 20% of subjects 70 years or older (both genders). Male subjects were younger overall, but had a higher prevalence of diabetes, hypertension, and proteinuria than did female subjects. The prevalence of eGFR less than 60 ml/min per 1.73 m^2 was about 16%. The distribution of eGFR according to gender is shown in Fig. 1. As expected, the prevalence of anemia in women increased from 4.4% to 7.3% when the JSDT anemia criteria were applied; consequently the overall prevalence was 7.4% in overall subjects.

Relationship between kidney function and hematocrit

Table 2 shows the mean hematocrit levels and prevalence of anemia according to BMI category, age category, and eGFR category for men and women. The lower the BMI category or the higher the age category, the lower the mean hematocrit level and the greater the prevalence of anemia. At age 70 years, the prevalence of anemia was clearly high. The mean hematocrit levels decreased and the prevalence of anemia increased as kidney function decreased below an

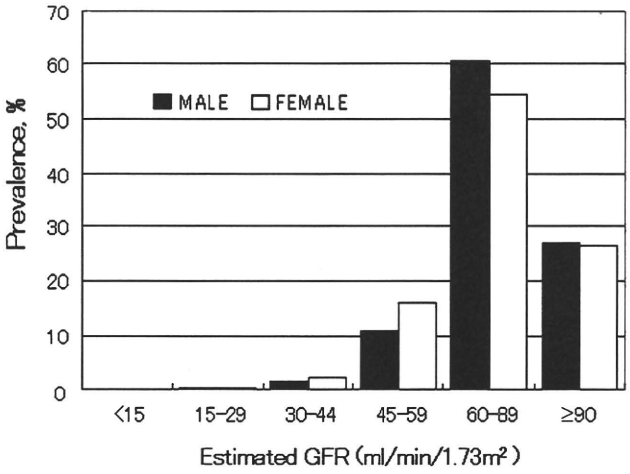

Fig. 1 Distribution of the estimated glomerular filtration rate in the cohort

eGFR of 60 ml/min per 1.73 m^2 among both men and women. In women, prevalence of anemia was 4.7% (age 20–29 years), 12.4% (age 30–39 years), 14% (age 40–49 years), 10.5% (eGFR ≥90 ml/min per 1.73 m^2), 5.7%

Table 2 Hematocrit levels and prevalence of anemia by clinical characteristics

	All ($N = 94,602$)			Men ($N = 39,754$)			Women ($N = 54,848$)		
	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)
BMI (kg/m^2)									
≥26	24367	42.3 ± 4.0 (ref)	664 (2.7)	10422	45.5 ± 3.0 (ref)	317 (3.0)	13945	40.0 ± 2.8 (ref)	347(2.5)
24–26	20942	41.9 ± 4.0*	921 (4.4)	96651	44.9 ± 3.0*	489 (5.1)	11281	39.4 ± 2.9*	432 (3.8)
22–24	22287	41.3 ± 4.1*	1325 (5.9)	9645	44.4 ± 3.2*	726 (7.5)	12642	38.9 ± 2.9*	599(4.7)
<22	26241	40.3 ± 4.0*	2429 (9.3)	9754	43.4 ± 3.6*	1471(15.0)	16487	38.5 ± 3.0*	958(5.8)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Age (years)									
20–29	5423	42.8 ± 4.3 (ref)	53(1.0)	2773	46.1 ± 2.7 (ref)	32(1.2)	2650	39.4 ± 2.6 (ref)	21(0.8)
30–39	11802	41.9 ± 4.7*	294 (2.5)	5746	46.7 ± 2.8*	99 (1.7)	6056	38.3 ± 3.0*	195(3.2)
40–49	17612	41.3 ± 4.7*	671 (3.8)	7723	45.3 ± 2.9*	210 (2.7)	9889	38.2 ± 3.3*	461(4.7)
50–59	19996	41.6 ± 3.7*	811 (4.1)	7684	44.7 ± 3.0*	340 (4.4)	12312	39.7 ± 2.7#	471(3.8)
60–69	22446	41.5 ± 3.6*	1306 (5.8)	9035	44.0 ± 3.2*	833 (9.2)	13411	39.7 ± 2.7§	473(3.5)
≥70	17323	40.5 ± 3.8*	2320 (13.4)	6793	42.6 ± 3.8*	1542 (22.7)	10530	39.2 ± 3.1	778(7.4)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Estimated GFR (ml/min per 1.73 m^2)									
≥90	25258	41.4 ± 4.4 (ref)	1084 (4.3)	10709	45.0 ± 3.0 (ref)	459 (4.3)	14549	38.7 ± 3.1 (ref)	625 (4.3)
60–89	54042	41.7 ± 4.0*	2836 (5.3)	24100	44.6 ± 3.3*	1741 (7.2)	29942	39.4 ± 2.9*	29942 (3.7)
45–59	13287	40.8 ± 3.8*	1115 (8.4)	4360	43.6 ± 3.8*	642 (14.7)	8927	39.4 ± 2.9*	473 (5.3)
30–44	1829	39.6 ± 4.0*	331 (18.1)	524	41.9 ± 4.5*	174 (33.2)	1305	38.7 ± 3.4	157 (12.0)
15–29	151	37.4 ± 5.0*	60 (39.7)	47	39.2 ± 5.9*	27 (57.5)	104	36.6 ± 4.5*	33 (31.7)
<15	35	31.5 ± 4.9*	29 (82.9)	14	31.6 ± 4.8*	13 (92.9)	21	31.5 ± 5.0*	16(76.2)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$

* <0.0001, # <0.05, § <0.0005

(eGFR 60–89 ml/min per 1.73 m^2), 5.9% (eGFR 45–59 ml/min per 1.73 m^2), 12.3% (eGFR 30–44 ml/min per 1.73 m^2), 32.7% (eGFR 15–29 ml/min per 1.73 m^2), and 81.0% (eGFR <15 ml/min per 1.73 m^2) when JSDT anemia criteria were applied.

Kidney function and the odds ratio of anemia

We performed multiple logistic analyses adjusted for older age (70 years and older) and BMI category to further assess the effect of decreased kidney function on anemia. Lower eGFR was found to be significantly associated with higher prevalence of anemia below eGFR of 90 ml/min per 1.73 m^2 in men and of 45 ml/min per 1.73 m^2 in women (Fig. 2). The odds ratios (ORs) of eGFR categories (ref, eGFR ≥90 ml/min per 1.73 m^2) overall, in men, and in women were as follows: eGFR 60–89 ml/min per 1.73 m^2: 1.150 (1.067–1.240, $P = 0.003$), 1.536 (1.374–1.717, $P < 0.0001$), and 0.857 (0.772–0.950, $P < 0.0001$); eGFR 45–59 ml/min per 1.73 m^2: 1.526 (1.385–1.681, $P < 0.0001$), 2.278 (1.979–2.622, $P < 0.0001$), and 1.076 (0.940–1.233, $P = 0.2885$); eGFR 30–44 ml/min per 1.73 m^2: 2.976 (2.564–3.454, $P < 0.0001$), 5.117 (4.072–6.431, $P < 0.0001$), and 2.265 (1.843–2.783, $P < 0.0001$); eGFR 15–29 ml/min per 1.73 m^2: 11.346 (7.909–16.276, $P < 0.0001$), 24.404 (12.710–46.857, $P < 0.0001$), and 8.234 (5.269–12.867, $P < 0.0001$); and eGFR ≤15 ml/min per 1.73 m^2: 104.250 (41.632–261.049, $P < 0.0001$), 288.024 (36.039–2301.922, $P < 0.0001$), and 65.386 (23.265–183.767, $P < 0.0001$). The OR of older age (over 70 years) was 2.772 (2.597–2.959, $P < 0.0001$) overall, 3.850 (3.531–4.198, $P < 0.0001$) in men, and 1.698 (1.530–1.884, $P < 0.0001$) in women. Additionally, the ORs of BMI categories (ref. BMI ≥26 kg/m^2) overall, in men, and in women were as follows: BMI 24–26 kg/m^2: 1.565 (1.412–1.735, $P < 0.0001$), 1.552 (1.339–1.798, $P < 0.0001$), and 1.580 (1.367–1.826, $P < 0.0001$); BMI 22–24 kg/m^2: 2.159 (1.960–2.377, $P < 0.0001$), 2.305 (2.007–2.648, $P < 0.0001$), and 1.959 (1.710–2.244, $P < 0.0001$); BMI <22 kg/m^2: 3.571 (3.264–3.907 $P < 0.0001$), 4.543 (3.991–5.171, $P < 0.0001$), and 2.466 (2.172–2.800, $P < 0.0001$).

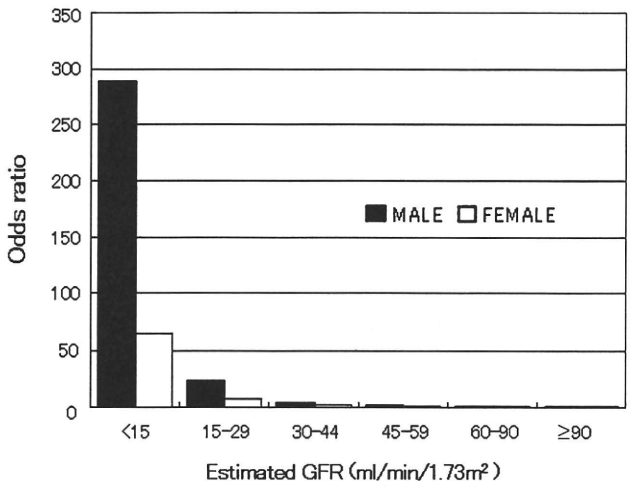

Fig. 2 Odds ratio of anemia by sex, adjusted for body mass index category and older age (>70 years) according to estimated glomerular filtration rate category in both sexes. Reference is eGFR ≥90 ml/min per 1.73 m^2

Prevalence of stage 3–5 CKD complicated with anemia

The result of the present study showed that 10% of subjects with stage 3–5 CKD were complicated with anemia. Since it has been estimated that there are 10,000,000 Japanese people with stage–3–5 CKD by using a new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female) [18], there could be as many as 1,000,000 Japanese people with stage 3–5 CKD complicated with anemia.

Discussion

Anemia is often associated with decreased eGFR. However, previous reports have suggested that the relationship between decreased kidney function and anemia varies across countries and races [15, 16, 23]. In the present study, which was conducted among a general Japanese population, the effect of decreased kidney function on anemia was significantly prevalent below eGFR of 90 ml/min per 1.73 m^2 in men and 45 ml/min per 1.73 m^2 in women.

As the previous study demonstrated [12], the distribution of eGFR among the general Japanese population is shifted to the lower side compared with that of the general US population [17]: the mean eGFR value was approximately 79 ml/min per 1.73 m^2 in our cohort, while it is reported to be 93 ml/min per 1.73 m^2 in the USA [17]. The higher incidence of aged subjects might be responsible for the lower eGFR value in Japan. Alternatively, the normal kidney function of the Japanese population might be fundamentally less than that of Caucasian populations due to the relatively smaller size of kidney and lower intake of protein. Regardless of its cause, a cutoff value of eGFR for clinical relevance is yet to be determined for the Japanese population. Some researchers have argued that it would be approximately 50 ml/min per 1.73 m^2 since the risk of end-stage renal disease (ESRD) increases significantly at this level [25]. In the present study, the OR of anemia increased to more than twice at eGFR values of less than approximately 50 ml/min per 1.73 m^2. According to the present study, the adjusted OR of stage 3 CKD for anemia in the Japanese general population has been shown to be around

two, which is similar to that in the general US population [16]. In terms of risk for complicating anemia, the clinical eGFR value in Japan might be similar to that of the general US population.

In the US population in the Third National Health and Nutrition Examination Survey (NHANES III), it was shown that African–Americans had a significantly higher OR (2.5) for anemia than Caucasians [16]. In another study from Italy conducted among patients whose mean age was about 75 years, the threshold of kidney function as a risk factor of anemia was found to be 30 ml/min per 1.73 m^2, which is lower than that of Japanese and US populations [24]. Although age might be responsible for the difference in the threshold level of kidney function in the Italian study, we found no such difference between subjects 70 years and older, and those under 70 years old (data not shown). Some factors, including differences in the definition of anemia and/or race, may affect this discrepancy.

In addition to racial differences, there might also be gender differences in the rate of complication with anemia at the same degree of kidney function. In the present study, men had a higher incidence and OR for anemia compared with women at eGFR values below 60 ml/min per 1.73 m^2; this is consistent with the previous report by Hsu et al. [25]. Differences in the cause of CKD between genders [26] and the effect of sex hormones on erythrogenesis might be responsible for this gender difference [27, 28].

The combination of anemia and CKD is reported to have a significant impact on survival compared with either anemia alone or CKD alone [29]. Since anemia has been identified not only as a nonclassical cardiovascular risk factor but also as a progressive factor in decreasing kidney function, anemia might play a significant role in the association between CKD and CVD. Accordingly, intervention for anemia could be an effective approach to prevent CVD in CKD subjects. However, large randomized intervention studies [30, 31] and a meta-analysis [32] have shown a slight but significant benefit of lower hemoglobin levels; it would thus be better to maintain these lower levels rather than attempt to improve outcome by achieving higher hemoglobin levels in CKD patients. Since the higher hemoglobin target group showed itself to have a higher risk of poorly controlled blood pressure [32], the clinical benefits of correction of anemia via an erythropoiesis-stimulating agent should be determined under strict control of blood pressure. Considering the substantial number of patients complicated with CVD and related death before starting hemodialysis therapy, intervention during ESRD might be too late to effectively prevent CVD. The incidence of anemia appears to increase from an eGFR of less than 60 ml/min per 1.73 m^2, as shown in previous studies [16] as well as in the present study. Therefore, intervention for anemia in the early stages of CKD could be an effective method of preventing CVD among CKD subjects.

In Japan, incidence of CKD is predicted to be much higher than that in the US population [12, 17]. Furthermore, it will increase since the number of elderly people is predicted to increase in Japan, at least during the next two decades. According to the present study, an association of kidney function with anemia was similar to that in the US population. Therefore, it is critical to screen CKD subjects for anemia.

The present study has a number of important limitations. First, we were unable to identify any causal association between decreased kidney function and anemia due to the cross-sectional design of the study. It was not clear how long-term CKD contributes to anemia at each CKD stage. We cannot exclude the possibility that other factors such as iron deficiency, malnutrition, and chronic disease might affect anemia. Second, one-third of the total cohort was excluded because of lack of data for Scr and Ht. It is possible that those with known kidney diseases and/or comorbid individuals are selected. However, the total number of subject is more than 90,000 and therefore it is subtle as a community-based cohort. Third, the results might vary according to the definition of anemia. The assessment of anemia by hematocrit may not be always precise and may be affected by volume status. Previous studies investigating the relationship between renal function and anemia have used the World Health Organization (WHO) criteria to define anemia [15, 16]. The WHO defines anemia as hemoglobin concentration of less than 12 g/dl for women and less than 13 g/dl for men. However, these criteria have physiological correlates in younger individuals. Therefore, it has been suggested that it might be inappropriate to apply these criteria to the present cohort, which included a substantially high number of older subjects [33]. Thus, it might be preferable to use the definition of anemia, which takes both age and sex into account [20, 21].

In conclusion, the threshold level of kidney function, below which there is an increased risk of more than twice for complicating anemia, was found to be an eGFR of approximately 50 ml/min per 1.73 m^2 in a general Japanese population. Therefore, there is expected to be a substantial number of CKD subjects with anemia who could have a higher risk for CVD as well as ESRD. Further information is needed to determine how and when intervention should be initiated in patients with both CKD and anemia.

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References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;51:1296–305.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama study. Kidney Int. 2005;68:228–36.
4. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, et al. Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (ARIC) study. J Am Coll Cardiol. 2002;40:27–33.
5. Jurkovitz CT, Abramson JL, Vaccarino LV, Weintraub WS, McClellan WM. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol. 2003;14:2919–25.
6. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol. 2005;16:529–38.
7. Leeder SR, Mitchell P, Liew G, Rochtchina E, Smith W, Wang JJ. Low hemoglobin, chronic kidney disease, and risk for coronary heart disease-related death: the Blue Mountains eye study. J Am Soc Nephrol. 2006;17:279–84.
8. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int. 2003;64:610–5.
9. Silverberg D, Wexler D, Blum M, Wollman Y, Iaina A. The cardio-renal anaemia syndrome: does it exist? Nephrol Dial Transplant. 2003;18(Suppl 8):viii7–12.
10. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, et al. Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. J Am Soc Nephrol. 2005; 16:180–8.
11. Meisinger C, Doring A, Lowel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. Eur Heart J. 2006;27:1245–50.
12. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11:156–63.
13. Chen J, Wildman RP, Gu D, Kusek JW, Spruill M, Reynolds K, et al. Revalence of decreased kidney function in Chinese adults aged 35 to 74 years. Kidney Int. 2005;68:2837–45.
14. Fehr T, Ammann P, Garzoni D, Korte W, Fierz W, Rickli H, et al. Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. Kidney Int. 2004;66:1206–11.
15. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol. 2002;13:504–10.
16. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med. 2002;162:1401–8.
17. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41:1–12.
18. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised Equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009; (in press).
19. Iseki K, Kinjo K, Iseki C, Takishita S. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. Am J Kidney Dis. 2004;441:806–14.
20. Gejyo F, Saito A, Akizawa T, Akiba T, Sakai T, Suzuki M, et al. 2004 Japanese Society for dialysis therapy guidelines for renal anemia in chronic hemodialysis patients. Ther Apher Dial. 2004;37:1737–63.
21. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative, Am J Kidney Dis. 1997; 30(4 Suppl 3):S192–240.
22. JSDT guideline for renal anemia in chronic kidney disease (2008). (http://www.jsdt.or.jp in Japanese).
23. Ble A, Fink JC, Woodman RC, Klausner MA, Windham BG, Guralnik JM, et al. Renal function, erythropoietin, and anemia of older persons: the InCHIANTI study. Arch Intern Med. 2005; 165:2222–7.
24. Imai E, Horio M, Yamagata K, Iseki K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Hypertens Res. 2008;31:433–41.
25. Hsu CY, Bates DW, Kuperman GJ, Curhan GC. Relationship between hematocrit and renal function in men and women. Kidney Int. 2001;59:725–31.
26. Iseki K, Nakai S, Shinzato T, Nagura Y, Akiba T. Increasing gender difference in the incidence of chronic dialysis therapy in Japan. Ther Apher Dial. 2005;9:407–11.
27. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. Am J Kidney Dis. 2006;47:251–62.
28. Mukundan H, Kanagy NL, Resta TC. 17-beta estradiol attenuates hypoxic induction of HIF-1alpha and erythropoietin in Hep3B cells. J Cardiovasc Pharmacol. 2004;44:93–100.
29. Silverberg DS, Wexler D, Blum M, Schwartz D, Wollman Y, Iaina A. Erythropoietin should be part of congestive heart failure management. Kidney Int Suppl. 2003;87:S40–7.
30. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355:2071–84.
31. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085–98.
32. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet. 2007;369:381–8.
33. Chaves PH, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? J Am Geriatr Soc. 2002;50:1257–64.

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Chronic kidney disease (CKD) and Kampo medicine

Chronic kidney disease (CKD): management and outcome improvement

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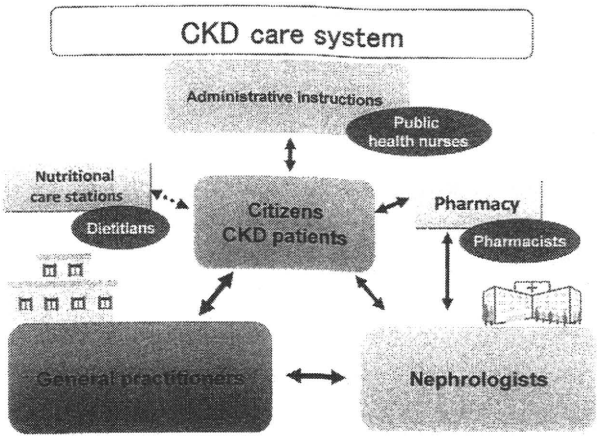
Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) <60ml/min/1.73m2 for 3 months or more, irrespective of cause. The definition of CKD first appeared in the Kidney Disease Outcome Quality Initiative Guidelines (KDOQI) issued by the National Kidney Foundation (NKF) in 2002,[1] and was revised by the KDIGO in 2005.[2] Since then, the definition of CKD and renal function assessment methods are accepted worldwide.

CKD is also one of the important risk factors for cardiovascular disease among known other risk factors; diabetes, hypertension, hyperlipidemia, obesity, smoking, and lifestyle-related diseases.[3,4] Therefore, the early detection and control of CKD are exactly important in terms of preventing ESKD, cardiovascular complications and death.

The concept of CKD is comprehensive which includes diabetic nephropathy, nephrosclerosis due to hypertension, chronic glomerulonephritis and other renal diseases. Since there are many patients with CKD, not only nephrologists but also all physicians, should care CKD patients for early detection and treatment at early stage. And it is important to establish appropriate, consistent, and specific treatment and prevention-based care system according to the progression of kidney disease.

Recently, the CKD Clinical Practice Guide was published by the Japanese Society of Nephrology[5] and treatment target for every CKD stage had been shown. From this guide, lifestyle and dietary advice on obesity prevention, smoking cessation, a sodium-restricted diet, treatment for metabolic disorders, hypertension, and hyperlipidemia are recommended to prevent the progression of CKD. Although every single item of the treatment method had clinical evidences, there was no prospective study to show the effect of practices as combination of CKD Clinical Practice Guide targets on renal and cardiovascular outcome in certain number of the CKD patients.

A strategic outcome research project for kidney disease has started in Japan since 2007, supported by a grant from the Ministry of Health, Labor and Welfare of Japan. This study has been designed to encourage CKD patients to consult physicians consecutively, enhance cooperation between general practitioners and nephrologists, and prevent the progression of kidney disease. If effective collaboration is established, it will have a significant positive impact on renal care systems (Figure)



Figure

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and improve outcomes of CKD patients. This study is expected to develop the infrastructure required for clinical practice of kidney disease, and to generate valuable findings.

References

1) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis,* **39**, S1-266, 2002.
2) Levey, AS., Eckardt, KU., Tsukamoto, Y., et al.: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int,* **67**, 2089-2100, 2005.
3) Yamagata, K., Ishida, K., Sairenchi, T., et al.: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int,* **71**, 159-166, 2007.
4) Go, AS., Chertow, GM., Fan, D., McCulloch, CE. and Hsu, CY.: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med,* **351**, 1296-1305, 2004.
5) CKD Clinical Practice Guide: Japanese Society of Nephrology (written and edited), First edition, Tokyo Igakusha, 2007.

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ORIGINAL ARTICLE

Design and methods of a strategic outcome study for chronic kidney disease: Frontier of Renal Outcome Modifications in Japan

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Abstract

Background The continuous increase in the number of people requiring dialysis is a major clinical and socioeconomical issue in Japan and other countries. This study was designed to encourage chronic kidney disease (CKD) patients to consult a physician, enhance cooperation between nephrologists and general practices, and prevent the progression of kidney disease.

Methods Subjects comprise CKD patients aged between 40 and 74 years consulting a general physician, and patients in CKD stage 3 with proteinuria and diabetes or hypertension. This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four

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regions (strata) based on the level of increase rate of dialysis patients. The patients in group A clusters were instructed initially to undergo treatment in accordance with the current CKD treatment guide, whereas patients in group B clusters were not only instructed in the same fashion but also received support from an information technology (IT)-based system designed to help achieve the goals of CKD treatment, consultation support centers, and consultations by dietitians visiting the local general practice offices. We assessed the rates of continued consultation, collaboration between general practitioners and nephrologists, and progression of CKD (as expressed by CKD stage).

Conclusion Through this study, filling the evidence-practice gap by facilitating effective communication and supporting general physicians and nephrologists, we will establish a CKD care system and decrease the number of advanced-stage CKD patients.

Keywords Chronic kidney disease · Evidence-practice gap · Cluster-randomized study · Educational intervention · Cooperation between nephrologists and general physicians

Introduction

The number of dialysis patients is continually increasing, with consequent rises in medical costs for the treatment of end-stage kidney disease (ESKD) patients becoming a socioeconomical concern worldwide. In fact, there are 2,153.2 dialysis patients per million of population in Japan [1]. Chronic dialysis treatment not only reduces the quality of life (QOL) of patients [2, 3] but also places considerable financial strain on society, with annual medical costs of five to six million yen per dialysis patient, or total expenses of one trillion yen. Moreover, it is estimated that there are more than ten million chronic kidney disease (CKD) patients in Japan [4]. Previous studies suggested that CKD is one of the most important risk factors for cardiovascular disease, among known risk factors of diabetes, hypertension, hyperlipidemia, obesity, smoking, and lifestyle-related disease [5–8]. Therefore, early detection and control of CKD are also important in terms of preventing cardiovascular complications and deaths.

The definition of CKD first appeared in the Kidney Disease Outcome Quality Initiative (KDOQI) Guidelines issued by the National Kidney Foundation (NKF) in 2002 [9], and was revised by Kidney Disease: Improving Global Outcomes (KDIGO) in 2005 [10]. Since then, the definition of CKD and renal function assessment methods are being accepted worldwide. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. The concept of CKD comprehensively addresses a wide range of kidney patients, including ESKD and transplant patients. It is important to establish appropriate, consistent, and specific treatment and prevention-based care systems according to the progression of kidney disease. The Ministry of Health, Labor, and Welfare organized a study group to design strategic outcome studies and discuss the following research subjects: prevention of diabetes, prevention of suicide and depression (2005), cancer prevention, and AIDS/HIV prevention (2006), which have been started. Following these studies, a strategic study to improve the progression of CKD was planned based on these social and scientific demands to reduce new patients with initiation of renal replacement therapy due to ESKD, termed the Frontier of Renal Outcome Modifications in Japan (FROM-J).

Diabetic nephropathy, nephrosclerosis due to hypertension, and chronic glomerulonephritis are three major primary renal diseases in ESKD, not only in Japan but also in Western countries [1]. In Japan, the proportion of new ESKD patients due to chronic glomerulonephritis has recently been decreasing, while that of diabetic nephropathy is rapidly increasing. If this trend continues, in 5 years, patients undergoing dialysis due to diabetic nephropathy will account for 50.82% of the total whereas those with chronic glomerulonephritis will account for 19.54%. In other words, the primary renal disease in half of dialysis patients will be diabetic nephropathy, and the number of dialysis patients with chronic glomerulonephritis will decrease by 17%. The decreasing trend in chronic glomerulonephritis is due to annual urinalysis screening programs established by the Japanese government [11]. Also, more attention should be paid to preventing deterioration of renal function in patients with diabetic nephropathy and nephrosclerosis.

Although diabetic nephropathy is the primary underlying disease in dialysis patients in many developed countries, it has been showing a decreasing trend in some regions and countries, including Denmark. In Denmark, after a steady increase from 52 in 1990 to 183 in 2002, the number of dialysis patients with diabetic nephropathy decreased by 15%, to 155–156 patients per million people [12]. This indicates that aggressive management of both blood pressure and glucose, administration of renin angiotensin system (RAS) inhibitors, and advice on lifestyle can reduce ESKD with diabetic nephropathy by more than 15%. According to the 2002 diabetes survey conducted by the Ministry of Health, Labor, and Welfare of Japan, only 33.3% of patients in Japan had controlled their HbA1c to less than 6.5%, and these interventions are expected to achieve marked effects. Furthermore, although 50.2% of males and 38.3% of females aged 40 years or

older in Ibaraki Prefecture showed hypertension, only 41.9% and 49.2% of them, respectively, were receiving antihypertensive treatment [13], and blood pressure was not adequately controlled in about 50% of those who were receiving treatment [14]. Appropriate interventions are assumed to bring about noticeable effects in Japan, in which RAS inhibitors have not been used effectively as antihypertensive therapy, although a slight increase has occurred in recent years [15].

Recently, the CKD Clinical Practice Guide for future treatment methods was developed by the Japanese Society of Nephrology [16], describing the treatment target for every CKD stage. Although all items of the treatment method were supported by clinical evidence, there were no prospective studies showing the effect of practices such as the CKD Clinical Practice Guide targets on renal and cardiovascular outcomes in sufficient number of CKD patients.

In this strategic CKD study, a prospective stratified cluster-randomized trial to examine the effectiveness of a care system designed to prevent progression of CKD through collaboration between nephrologists and general physicians was selected. One of the goals of the study is a 15% reduction in the estimated number of new dialysis patients in 5 years by increasing the rates of compliance with the CKD Clinical Practice Guide. The study also aims to encourage CKD patients to see their family physician, consult a nephrologist, and receive nutritional and lifestyle advice, while discussing health care measures to reduce the number of new dialysis patients.

Hypotheses of study

The study hypothesis encompasses the following four core issues:

1. Clinical practice in accordance with the Japanese CKD Clinical Practice Guide will improve the prognosis of CKD patients and reduce the speed of renal function deterioration.
2. Education-based interventions for CKD patients by registered dietitians and other co-medicals will help achieve strict CKD treatment goals in accordance with the Japanese CKD Clinical Practice Guide.
3. Collaboration concerning clinical practices among general physicians, nephrologists, and co-medicals will reduce the gap between clinical practice and evidence-based care measures, and improve the rate of continued consultation and prognosis in CKD patients.
4. These active interventions to improve CKD treatment will achieve the desired effects in terms of medico-economics.

Subjects and methods

Study organization and duration

Since the increase in the rate of dialysis patients varies from region to region in Japan [17], we divided the country into four regions (Fig. 1) as strata, so that they would

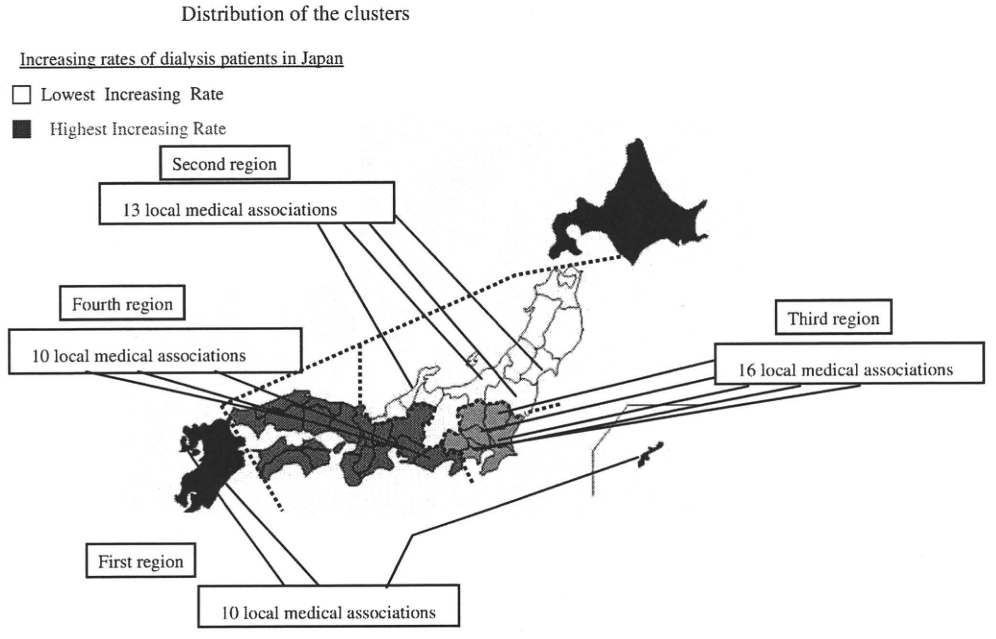

Fig. 1 Distribution of the clusters. We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients [17]

include at least one managing facility and two or more clusters. The primary intervention study duration is from October 2008 to March 2012.

Rationale for setting the number of patients

This project aims to examine whether or not intervention can reduce the incidence of dialysis patients by 15% over the next 5 years. Regarding the calculation, we estimated the annual decrease in GFR as 0.59 ml/min/year (standard deviation (SD) 0.04 ml/min/year), based on changes in renal function among healthy Japanese people who underwent health checkups [17, 18] and the rate of renal deterioration in patients in CKD stage 3 with diabetes or hypertension [mean serum creatinine = 1.69 mg/dl (SD = 0.57 mg/dl), annual decrease rate = 5.93 ml/min/year (SD 4.321 ml/min/year), $n = 569$] [18, 19]. The required study size was calculated as 2,038 when the unknown intracluster correlation coefficient was assumed to be 0.5. We determined the required number as 2,264 for groups A and B, assuming that 10% would withdraw. We applied the simple number of 2,500 (1,250 for each group) as the target number of patients to perform this study.

Eligible patients

Each registered general physician obtained written informed consent for the study from eligible patients. They were formerly registered after the data center verified their eligibility. Inclusion criterion were: (1) age between 40 and 74 years; (2) in CKD stage 1, 2, 4, or 5; (3) in CKD stage 3 with proteinuria (ratio of urinary protein/urinary creatinine $\geq$0.3, or proteinuria $\geq$1+) and diabetes or hypertension.

Dialysis patients and those who did not consent were excluded from this study.

Assignment and randomization

This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients (Fig. 1). Each local medical association recruited 10–58 general physicians by whom patients in this study has been treated. Local medical associations are randomized when the enrolment period is completed.

Intervention methods

Patients in group A clusters are instructed initially to undergo treatment in accordance with the current CKD treatment guide only, whereas patients in group B clusters are not only instructed in the same fashion but also receive consultations by dietitians visiting the local general practice offices. In addition, the data center closely monitors the treatment status and provides the group B general practice office with comments on the data.

Goals for the treatment of chronic kidney disease (groups A and B)

Participants in the study, or patients, will receive treatment according to the CKD Clinical Practice Guide [16]. Table 1 shows a summary of targets for CKD treatment applied to all patients. In patients with CKD, lifestyle modifications to avoid obesity and stop smoking are necessary. Strict blood pressure control (less than 130/80 mmHg), strict blood sugar control (HbA1c <6.5%), and low-density lipoprotein (LDL)-cholesterol control (LDL-C <120 mg/dl) are shown as targets for CKD treatment. The standards for referral from general physicians to nephrologists are as follows: (1) ratio of urinary protein/urinary creatinine $\geq$0.5, or proteinuria $\geq$1+; (2) estimated GFR (eGFR) <50 ml/min/1.73 m^2; (3) both proteinuria and hematuria positive ($\geq$1+); and (4) when family physicians judge that patients should consult a nephrologist. Estimated GFRs in this study are calculated using the following formula:

$$\mathrm{eGFR(ml/min/1.73\ m^2)} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cre}^{-1.094} (\times 0.739 \text{ in the case of women}).$$

Monitoring of treatment status by the data center (only group B)

The data center closely monitors the treatment status and provides the group B general practice office with comments on the data. In addition, the data center will provide information on the patients scheduled to visit the office, examinations, and treatment that patients should undergo on their next visit, patients who did not visit hospitals as scheduled, those who are going to receive lifestyle/dietary advice, and those who meet the conditions for referral to nephrologists. The center also monitors patients and their schedules: the next consultation date, required examinations, details of treatment and care provided, and advice on lifestyle and nutrition. The centers will contact patients by mail, telephone, or email a week before the consultation day and encourage those who have not consulted a physician for over 2 months to receive care, trying to prevent their withdrawal from treatment. To facilitate referrals to nephrologists, the centers send a list of patients who meet the criteria for referral to the physicians and clinical research coordinators (CRCs).

Table 1 CKD practice guide target in this study

CKD stages	Lifestyle	Diet	Blood pressure	Blood sugar	Lipid metabolism	Hemoglobin
Stage 1	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 2	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 3	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 4	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 5	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Others			<125/75 mmHg If proteinuria >1 g/day			

BMI body mass index, *DPI* dietary protein intake

Nutrition and lifestyle improvement (only group B)

Registered dietitians provide support according to the instructions and advice from family physicians. They help patients achieve their CKD treatment goals, explaining to patients about examination results, achievements in CKD care, and their implications. Registered dietitians receive training so that they will be able to provide integrated and consistent advice.

Data collection

At each consultation, physicians will measure patients' blood pressure, and check their blood pressure conditions at home. Examinations or surveys will be performed every 6 months regarding body weight, abdominal circumference, smoking status, fasting serum creatinine, blood urea nitrogen (BUN), potassium, hemoglobin (Hb), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), uric acid, total protein, albumin, fasting blood glucose, HbA1c (only in the case of diabetes), urinary creatinine levels, amount of urinary proteins, eGFR, number of patients referred by nephrologists, number of new dialysis patients, and incidence of cardiovascular events.

Parameters for assessment

Primary parameters for assessment are: (1) the rate of continuous clinic visits of CKD patients, (2) the proportion of patients under cotreatment between general physicians and nephrologists, and (3) annual changes in CKD stage.

Secondary parameters are: (1) the proportion of adherence to the complete CKD treatment guide, (2) the rate of achievement of blood pressure goals, (3) the number of subjects with 50% reduction in urinary protein, (4) the number of subjects with a doubling of serum creatinine or 50% reduction in eGFR, (5) yearly changes in the number of patients starting renal replacement therapy, and (6) the incidence of cardiovascular events.

Statistical analysis

Statistical analyses will be performed using an intent-to-treat approach. Differences in primary endpoints between intervention groups are described by their 95% confidence intervals. The declining velocity of eGFR is tested by analysis of variance, using the efficacy of interventions as fixed effects and cluster effects as random effects. We employ a generalized linear model with age, gender, complications, and previous GFR as covariates where appropriate. The significance level on both sides in hypothesis testing is set at 0.05.

For secondary endpoints, we will use analysis of variance with a generalized linear model.

Ethical considerations

This study is being conducted in accordance with the Ethical Guidelines for Clinical Studies (revised on December 28, 2004, of the Ministry of Health, Labor, and Welfare) and the Ethical Guidelines for Epidemiological Studies (revised on August 16, 2007, of the Ministries of Education, Culture, Sports, Science, and Technology/ Health, Labor, and Welfare). All medical professionals involved in this study must comply with these ethical standards. This study is a Central Institutional Review Board (Central IRB) program, and the Committee on Ethics in Strategic Research of the Kidney Foundation, Japan, will examine and approve implementation plans and their revision.

Discussion

The purpose of this study is to enhance cooperation between nephrologists and general physicians, improve lifestyle and dietary advice provided by registered dietitians at general physicians' offices, and offer measures to control blood pressure and other critical parameters in practice, thereby filling the evidence-practice gap, which will slow the progression of kidney disease.

Recently, the concept of chronic kidney disease has been announced not only in Japan, but also throughout the world [9, 10]. There are more than ten million CKD patients in Japan [4], and so CKD is regarded as a public health problem.

CKD guidelines for general physicians or patients have been published in European countries [9, 20–22]. The USA is also preparing similar measures for CKD [23, 24]. In Japan, annual urinalysis for early detection of renal disease started in the 1970s [11, 25], and a serum creatinine test was included in health examinations as early as 1989 to detect kidney failure among adults aged 40 years or older [26]. However, the number of dialysis patients is increasing by approximately 4% each year. It is necessary to implement more appropriate measures to reduce the rate of new dialysis patients in Japan as soon as possible.

In 2007, the Japanese Society of Nephrology established the CKD Clinical Practice Guide to help family physicians provide care for CKD patients. The guide suggests that lifestyle and dietary advice on obesity prevention [27], smoking cessation [28], and a sodium-restricted diet, and treatment for metabolic disorders [29, 30], hypertension [31], and hyperlipidemia [32] are effective to prevent progression of CKD. However, most people are not making sufficient efforts to manage their own health condition [13]. It is necessary to show the effect on the progression of CKD of treatment as part of the Clinical Practice Guide. Our challenge is to obtain sufficient evidence regarding the efficacy of filling the evidence-practice gap in preventing deterioration of renal function among Japanese patients.

We set the following conditions for patient eligibility in this study: CKD patients aged between 40 and 74 years; patients in CKD stage 1, 2, 4 or 5; and patients in CKD stage 3 with a high level of urinary protein and diabetes or hypertension. Proteinuria is known as the strongest predictor of decreasing renal function [13, 33], and the aggressive management of blood pressure and glucose [29, 31] and administration of RAS inhibitors [34–36] prevent the deterioration of renal function. The reason for the condition regarding urinary proteins in stage 3 patients is that we need to register patients showing significant deterioration in renal function [37].

Regarding lifestyle and dietary advice, we have prepared a list of instructions and advice for individual patients on a priority basis, so that registered dietitians can design a guidance schedule based on the priority list and provide consistent advice. In this study, we focus on preventing progression of CKD in the early stage by giving priority to Japanese CKD practice guide goals. We are preparing a long-term guidance method covering a wide range of health management items while seeking ways to reduce the evidence-practice gap as much as possible.

We predict significant positive effects in intervention group B (increased collaboration in clinical practice) in terms of increases in the rate of continued consultation and collaboration between nephrologists and other physicians, and reduced CKD stage progression as a result of instructions and advice from registered dietitians, compared with intervention group A. This study was designed to examine the effectiveness of a support system for collaborative CKD diagnosis and treatment by conducting a cluster-randomized controlled trial. We expect that this study will help improve clinical practices for CKD patients and provide high-quality clinical findings of global standard. Although the number of CKD patients in Japan is estimated to be more than ten million, there are only 3,000 nephrologists. If effective collaboration is established among nephrologists in CKD care, it will have a significant positive impact on renal care systems. In the area of renal care, few large-scale intervention studies have been performed on kidney care systems, except those aimed to assess the efficacy of drug interventions. Little progress has been made in the development of infrastructure for clinical studies and research environments in Japan. This study is expected not only to help develop the infrastructure required for clinical renal studies but also to generate valuable findings.

Progress of the study

Prior to the study, we selected 15 management facilities and 49 local medical associations, registered 491 family physicians (between April and June 2008), and registered 2,494 study participants on a provisional basis (between April and October 15, 2008), 2,413 of whom were randomly divided into intervention groups A (1,211) and B (1,202) in units of medical associations (or clusters) in September 2008. We started the intervention study on October 20, 2008.

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References

1. Nakai S, Masakane I, Akiba T, Iseki K, Watanabe Y, Itami N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2005). Ther Apher Dial. 2007;11:411–41.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
4. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease (CKD) in Japanese general population. Clin Exp Nephrol, 2009.
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
8. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch Intern Med. 2005;165: 2659–65.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–266.
10. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
11. Yamagata K, Takahashi H, Suzuki S, Mase K, Hagiwara M, Shimizu Y, et al. Age distribution and yearly changes in the incidence of end-stage renal disease in Japan. Am J Kidney Dis. 2004;43:433–43.
12. Sorensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark. Kidney Int. 2006;70:187–91.
13. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71: 159–66.
14. Heagerty A. Optimizing hypertension management in clinical practice. J Hum Hypertens. 2006;20:841–9.
15. Usami T, Nakao N, Fukuda M, Takeuchi O, Kamiya Y, Yoshida A, et al. Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan. Kidney Int. 2003;64:1445–9.
16. CKD Clinical Practice Guidelines: Japanese Society of Nephrology (written and edited), First edition, Tokyo Igakusha, 2007.
17. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G. Regional variations in the incidence of end-stage renal failure in Japan. JAMA. 2000;284:2622–4.
18. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
20. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13): S289–91.
21. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med. 2005;5:635–42.
22. Nicholls K. Prevention of progression of kidney disease: diabetic nephropathy—CARI guidelines. Aust Fam Physician. 2007;36: 137–8.
23. IV. NKF-K/DOQI Clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis. 2001; 37:S182–238.
24. Neumann ME. Results in KEEP's first report show progress in early identification of CKD patients. Nephrol News Issues. 2003;17:84–7.
25. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. Nephron. 2002;91:34–42.
26. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
27. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis. 2006;48: 383–91.
28. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence?. Clin J Am Soc Nephrol. 2008;3:226–36.
29. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993; 329: 977–86.

30. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103–17.
31. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36:646–61.
32. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14:2084–91.
33. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
34. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939–45.
35. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis. 1999;34:809–17.
36. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
37. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90.

Therapeutic Apheresis and Dialysis

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An Overview of Regular Dialysis Treatment in Japan (As of 31 December 2007)

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Abstract: A nationwide statistical survey of 4098 dialysis facilities was conducted at the end of 2007, and 4052 facilities (98.88%) participated. The number of patients undergoing dialysis at the end of 2007 was determined to be 275 242, an increase of 10 769 patients (4.1%) compared with that at the end of 2006. The number of dialysis patients per million at the end of 2007 was 2154. The crude death rate of dialysis patients at the end of 2007 from the end of 2006 was 9.4%. The mean age of new patients begun on dialysis was 66.8 years and the mean age of the entire dialysis patient population was 64.9 years. For the primary diseases of new patients begun on dialysis, the percentages of patients with diabetic nephropathy and chronic glomerulonephritis were 43.4% and 23.8%, respectively. The percentages of facilities that achieved the control standard of endotoxin concentration in the dialysate solution of <0.05 EU/mL and those that achieved a bacterial count of <100 cfu/mL in the dialysate solution, as specified by the Japanese Society for Dialysis Therapy, were 93.6% and 97.4%, respectively. The percentage of patients positive for the hepatitis C virus antibody among the entire dialysis population significantly decreased from 15.95% at the end of 1999 to 9.83% at the end of 2007. The mean hemoglobin concentration in all the dialysis patients at the end of 2007 was 10.27 (±1.32, SD) g/dL, which has scarcely changed over the last three years. The numbers of male and female patients with a history of hip fracture were 142.9 and 339.0 per 10 000 dialysis patients, respectively, showing an extremely high prevalence among female patients. A history of hip fracture correlates with a low body mass index, serum albumin concentration, and a history of diabetes. The serum creatinine level of patients upon introduction to dialysis was 8.34 (±3.55) mg/dL, and the estimated glomerular filtration rate was 5.43 (±3.43) mL/min/1.73 m^2 for the patients who were newly begun on dialysis in 2007. **Key Words:** Clinical condition, Dialysis patient population, Endotoxin concentration, History of fracture, Survey, Survival rate.

The Japanese Society for Dialysis Therapy has been conducting a yearly statistical survey of dialysis facilities across the country since 1968. A nationwide statistical survey of 4098 dialysis facilities was conducted at the end of 2007, and 4052 facilities (98.88%) responded. The number of patients undergoing dialysis at the end of 2007 determined on the basis of the survey results from dialysis facilities was 275 242, an increase of 10 769 patients (4.1%) from the number in 2006. The crude death rate of dialysis patients in 2007 was 9.4%, which is not significantly different from those over the last 10 years (1).

In the first part of this report, we summarize basic data on chronic dialysis patients in Japan at the end of 2007; in the second part, we summarize data obtained from the same survey on the following items: the current status of dialysate solution quality control, hepatitis virus infection, and renal anemia therapy; the patient history of hip fracture; and the clinical conditions of patients at the introduction of

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