subjects was diagnosed as having metabolic syndrome, using the Japanese criteria, at baseline and seventeen subjects were diagnosed as having metabolic syndrome at the 1-year follow up. We have previously reported that the prevalence of metabolic syndrome was 30.7% in Japanese men [18]. In this study, with lifestyle modification after the initial health check-up, metabolic components were significantly improved in men without medications at the one year follow-up. Although eGFR and serum uric acid levels were not improved after one year, changes in eGFR were negatively correlated with changes in serum uric acid levels. Taken together, reducing serum uric acid levels such as medications may be useful for improving eGFR in Japanese men.

Higher serum uric acid levels contribute to the development of renal injury and end-stage renal disease [7-12]. Satirapoj B *et al.* reported in a cross-sectional study that high serum uric acid level was independently associated with increased prevalence of CKD in 5546 Southeast Asian population [7]. The age-adjusted odds ration for CKD, with subjects with no hyperuricemia and no metabolic syndrome, was 5.85 for subjects with both hyperuricemia and metabolic syndrome [8]. Yen CJ *et al.* also showed that serum uric acid levels were associated with eGFR and decline in renal function in elderly Taiwanese subjects by longitudinal analysis [9]. In Japanese, hyperuricemia, hypercholesterolemia and diabetes are risk factors for CKD in peripheral arterial disease [19]. In the present study, there was weak relationship between eGFR and serum uric acid levels at baseline. In addition, we revealed that, changes in serum uric acid levels were correlated with changes in eGFR in men without medications. Changes in other metabolic components, except abdominal circumference, were not linked to changes in eGFR. Therefore, the clinical impact of serum uric acid levels on eGFR was noted in Japanese men.

Potential limitations remain in our study. First, the small sample size in our study makes it difficult to infer causality between eGFR and serum uric acid levels. In addition, eGFR and serum uric acid levels were not increased with lifestyle modification after one year. Second, we also could not reveal the mechanism of the linkage between eGFR and serum uric acid levels. Third, most of the enrolled subjects were not diagnosed as CKD at baseline. Therefore, the results in this study may not apply for patients with CKD. Further prospective studies using medications are needed in Japanese subjects.

5. ACKNOWLEDGEMENTS

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Comparison of muscle strength between subjects with and without proteinuria

Nobuyuki Miyatake[1*], Kenichi Shikata[2,3], Hirofumi Makino[3], Takeyuki Numata[4]

[1]Department of Hygiene, Faculty of Medicine, Kagawa University, Miki, Kagawa, Japan;
[*]Corresponding Author: miyarin@med.kagawa-i.ac.jp
[2]Center for Innovative Medicine, Okayama University Hospital, Okayama, Japan;
[3]Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;
[4]Okayama Southern Institute of Health, Okayama Health Foundation, Okayama, Japan.

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ABSTRACT

We compared the levels of muscle strength between subjects with and without proteinuria. We used data of 721 men and 1063 women, aged 20 - 79 years, in this cross-sectional investtigation study. Parameters at muscle strength *i.e.* grip strength, leg strength and leg strength per body weight were evaluated. Proteinuria was measured by urine strip devices. Thirty five men (4.9%) and 27 women (2.5%) were diagnosed as having the proteinuria (+: 30 mg/dl) ≦). Leg strength and leg strength per body weight in men with proteinuria was significantly lower than that in men without proteinuria after adjusting for age. Grip strength in men with proteinuria was also lower than that in men without, but not at a significant level. However such link was not noted in women after adjusting for age. Among Japanese, proteinuria might be a modifiable factor of muscle strength in Japanese men.

Keywords: Proteinruia; Grip Strength; Leg Strength; Leg Strength per Body Weight

1. INTRODUCTION

Chronic kidney disease (CKD) has become a public health problem in Japan and it is a major risk factor for the end stage renal disease, cardiovascular disease and premature death [1,2]. About 20% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for at least three months regardless of cause [3]. We have previously showed in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [4] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [5]. In addition, we have also reported that proteinuria was closely linked to lower cardiorespilatory fitness evaluated by ventilatory threshold (VT) [6].

It is also well known that low and declining muscle strength is associated with increased mortality, independent of physical activity and muscle mass [7]. In 2006 in Japan, levels of maximal oxygen uptake and muscle strength were recommended as exercise and physical activity reference quantity for health promotion 2006 (EPARQ2006) by the Ministry of Health, Labor and Welfare [8]. Although resistance training has been advocated as the most suitable exercise for increasing muscle strength [9,10], the link between proteinuria and muscle strength in a large sample of Japanese has not yet been investigated.

In this study, we investigated muscle strength evaluated by grip strength, leg strength and leg strength per body weight between subjects with and without proteinuria in Japanese.

2. SUBJECTS AND METHODS

2.1. Subjects

We used all data on 1,784 Japanese (721 men and 1063 women) aged 20 - 79 years in a cross-sectional study. All subjects met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health checkup at Okayama Southern Institute of Health; 2) they had received muscle strength, urine examination and anthropometric measurements as part of their annual health checkups; and 3) they provided informed consent (**Table 1**).

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Table 1. Clinical profiles of enrolled subjects.

	Men			Women		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Number of subjects	721			1063		
Age	47.9 ± 15.1	20	78	44.7 ± 13.9	20	79
Height (cm)	169.7 ± 6.0	143.7	186.7	156.9 ± 5.3	140.4	172.9
Body weight (kg)	71.3 ± 11.8	39.1	146.5	55.8 ± 9.6	29.3	118.0
Body mass index (kg/m^2)	24.7 ± 3.7	13.6	43.1	22.7 ± 3.8	14.1	44.9
Abdominal circumference (cm)	86.5 ± 10.3	62.4	135.0	78.3 ± 10.9	55.1	127.0
Right grip strength (kg)	42.4 ± 7.7	3.4	70.2	25.6 ± 5.1	7.1	45.1
Left grip strength (kg)	40.4 ± 7.6	4.6	63.1	24.3 ± 4.9	4.5	43.5
Leg strength (kg)	67.1 ± 17.5	19.0	140.0	41.5 ± 11.2	11.0	79.0
Leg strength per body weight	0.95 ± 0.22	0.28	1.65	0.75 ± 0.19	0.17	1.46

The study was approved by the Ethics Committee of Okayama Health Foundation.

2.2. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level in standing subjects after normal expiration [11].

2.3. Muscle Strength

To assess muscle strength, grip and leg strength were measured [12]. Grip strength was measured using THP-10 (SAKAI, Tokyo, Japan), while leg strength was measured by COMBIT CB-1 (MINATO, Osaka, Japan). Isometric leg strength was measured as follows: the subject sat in a chair, grasping the armrest in order to fix the body position. A dynamometer was then attached to the subject's one ankle joint by a strap. The subject extended his or her leg to 60 degrees as described in previous reports [12,13] which have also demonstrated good accuracy for this measurement [13]. All muscle strength measurements were recorded in 2 trials, and the better one was employed for analysis. In addition, to standardize the influence of body weight, we calculated the ratio of leg strength to body weight; a ratio of 1.0 in leg strength per body weight has been a standard in past studies [13].

2.4. Urine Examination

Urine samples were collected from the second-morning urine (before 10 a.m.) and examined within 1 hour. The urine examination was performed using urine strip tests (BAYER, Tokyo, Japan). The reagent strip was dipped directly into the urine sample. Just after dipping, the sample is graded as −: negative, ±: trace positive, +: positive (30 mg/dl), 2+: positive (100 mg/dl), 3+: positive (300 mg/dl) or 4+: positive (1000 mg/dl) by comparison with a standard color chart found on the container's label [14].

2.5. Statistical Analysis

All data are expressed as mean ± standard deviation (SD) values. A statistical analysis was performed using an unpaired t test and covariance analysis, where $p < 0.05$ was considered to be statistically significant.

3. RESULTS

Clinical profiles are summarized in **Table 1**. Leg strength was 67.1 ± 17.5 kg in men and 41.5 ± 11.2 in women. Prevalence of proteinuria in enrolled subjects is also summarized in **Table 2**. A total of 35 men (4.9%) and 27 women (2.5%) was diagnosed as having the proteinuria (+: 30 mg/dl ≦).

We compared muscle strength between subjects with and without proteinuria (**Table 3**). In men, leg strength and leg strength per body weight in subjects with proteinuria was significantly lower than those in subjects without proteinuria even after adjusting for age by using covariance analysis (leg strength: $p = 0.0017$, leg strength per body weight: $p = 0.0495$). The significant differences of grip strength were not noted in men at a significant level (right grip strength: $p = 0.3691$, left grip strength: $p = 0.0670$). In women, parameters of muscle strength in subjects with proteinuria were not significant different from those in subjects without proteinuria (**Table 3**).

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Table 2. Prevalence of proteinuria in enrolled subjects.

Proteinuria	20's	30's	40's	50's	60's	70's	Total	%
Men								
−	72	120	132	138	124	25	611	84.7
±	7	18	13	12	18	7	75	10.4
+	4	3	3	6	4	3	23	3.2
2+	0	3	2	1	3	1	10	1.4
3+	0	0	0	0	1	0	1	0.1
4+	0	0	0	0	1	0	1	0.1
Total	83	144	150	157	151	36	721	
Women								
−	165	224	202	207	144	30	972	91.4
±	13	15	10	18	8	0	64	6.0
+	5	1	3	5	2	0	16	1.5
2+	2	1	3	0	0	2	8	0.8
3+	1	2	0	0	0	0	3	0.3
Total	186	243	218	230	154	32	1063	

Table 3. Comparison of muscle strength between subjects with and without proteinuria.

	Proteinuria (− or ±)	Proteinuria (+≦)	*p*	*p* After adjusting for age
Men				
Number of subjects	686	35		
Age	47.8 ± 14.1	51.3 ± 16.2	0.1553	
Right grip strength (kg)	42.6 ± 7.6	39.6 ± 9.9	**0.0284**	0.3691
Left grip strength (kg)	40.5 ± 7.5	37.8 ± 8.9	**0.0379**	0.0670
Leg strength (kg)	67.3 ± 17.2	62.9 ± 21.7	0.1509	**0.0017**
Leg strength per body weight	0.95 ± 0.22	0.83 ± 0.26	**0.0017**	**0.0495**
Women				
Number of subjects	1036	27		
Age	44.8 ± 13.9	42.3 ± 16.3	0.3519	
Right grip strength (kg)	25.7 ± 5.1	23.5 ± 5.0	**0.0294**	0.7149
Left grip strength (kg)	24.3 ± 4.9	22.7 ± 4.4	0.0877	0.6094
Leg strength (kg)	41.5 ± 11.2	40.9 ± 11.5	0.7804	0.4926
Leg strength per body weight	0.75 ± 0.19	0.71 ± 0.18	0.2672	0.8468

4. DISCUSSION

In this study, we firstly evaluated the link between proteinuria and muscle strength *i.e.* grip strength, leg strength and leg strength per body weight in Japanese. Proteinuria might be a modifiable factor of muscle strength, especially in Japanese men.

Proteinuria and/or reduced renal function have been reported to be closely linked to cardio vascular disease (CVD) [15,16]. Anavekar *et al.* showed that even mild renal disease was considered a major risk factor for CVD after myocardial infarction in 14527 patients with acute myocardial infarction [15]. Irie *et al.* reported that they evaluated 30,764 men and 60,668 women aged 40 - 79 years for 10 years, and proteinuria and hypercreatinemia or reduced GFR and their combination were sig-

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nificant predictors of CVD and all-cause mortality [16]. We have also reported that proteinuria was a modifiable factor for cardiorespilatory fitness evaluated by VT [6]. However, according to the link between proteinuria and muscle strength, there were few studies especially in Japan. Protein-energy wasting is the term proposed to describe the reduction in the stores of energy and protein in patients CKD [17]. Muscle wasting is one of the best markers of protein-energy wasting in these patients [18]. Leal *et al.* reported that handgrip strength is a useful tool for continuous and systematic assessment of muscle mass related to nutritional status in patients on dialysis [19]. Takhreen reviewed that relationship between exercise intervention and quality of life (QOL) in CKD patients. Exercising patients have shown improvements in physical fitness, psychological function, reaction times and lower extremity muscle strength, and these factors help improve QOL [20]. In this study, we solely evaluated the relationship between proteinuria and muscle strength *i.e.* grip strength, leg strength and leg strength per body weight in the Japanese. The significant differences of leg strength and leg strength per body weight between men with and without proteinuria even after adjusting for age. However, muscle strength in women with proteinuria was not significantly lower than that in women without.

Potential limitations still remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, 721 men and 1063 women in our study voluntarily underwent measurements: they were therefore more likely to be health-conscious compared with the average person. Second, we could not show clear mechanism between proteinuria and muscle strength. We have previously reported that brachial-ankle pulse wave velocity (baPWV) in subjects with reduced eGFR was significantly higher than that in subjects without [21]. In addition to protein-energy wasting, arterial stiffness might affect the results. Third, significant difference of muscle strength was not noted in women in this study. Low prevalence of proteinuria also affected the results, especially in women. To show this, further prospective studies are needed in the Japanese.

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The relation between estimated glomerular filtration rate (eGFR) and coffee consumption in the Japanese

Nobuyuki Miyatake[1*], Kenichi Shikata[2,3], Hirofumi Makino[3], Takeyuki Numata[4]

[1]Department of Hygiene, Faculty of Medicine, Kagawa University, Kagawa, Japan;
[*]Corresponding Author: miyarin@med.kagawa-i.ac.jp
[2]Center for Innovative Medicine, Okayama University Hospital, Okayama, Japan;
[3]Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;
[4]Okayama Southern Institute of Health, Okayama Health Foundation, Okayama, Japan.

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ABSTRACT

We investigated the link between estimated glomerular filtration rate (eGFR) and coffee consumption in Japanese. We used data of 376 men and 794 women who were not taking any medications, aged 20 - 78 years, in this cross-sectional investigation study. eGFR was calculated using serum creatinine (Cr), age and sex. Habitual coffee consumption was defined as drinking one or more cups of coffee per day. Two hundred thirty three men (62.0%) and 400 women (50.4%) were subjects with habitual coffee consumption (coffee consumption 1 cup/day ≥). eGFR was negatively correlated with age (men: r = –0.533, women: r = –624). eGFR in subjects with coffee consumers was not significantly different from that in subjects without coffee consumers after adjusting for age in both sexes (men: p = 0.1375, women: p = 0.2069). Among Japanese not taking medications, coffee consumption was not associated with eGFR in the Japanese population.

Keywords: Estimated Glomerular Filtration Rate (eGFR); Coffee Consumption; Creatinine; Japanese

1. INTRODUCTION

Coffee is one of the most common frequently consumed beverages and 10.6 coffee cups per week are reported to be consumed [1] and about 50% of Japanese drinks coffee daily [2]. Some studies showed that habitual coffee consumption may improve insulin resistance and abdominal glucose metabolism [3-5]. However, Tofovic *et al.* [6] have reported that prolonged consumption of caffeine has adverse effects on renal function, in high-renin hypertension.

Chronic kidney disease (CKD) has become a public health challenge and is a common disorder [7]. For example, about 20% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for at least three months regardless of cause [8]. We have also previously reported in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [9] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [10]. Therefore, the effect of coffee consumption on renal function may be required and it still remains to be investigated in Japanese.

In this study, we investigated renal function evaluated by eGFR in Japanese and evaluated the clinical impact of coffee consumption on eGFR in subjects not taking medications.

2. SUBJECTS AND METHODS

2.1. Subjects

We used all data on 1170 Japanese (376 men and 794 women) aged 20-78 years in a cross-sectional study. All subjects met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health checkup from April 2006 to December 2010 at Okayama Southern Institute of Health; 2) they had received creatinine (Cr), anthropometric measurements and evaluation of coffee consumption as part of their annual health checkups; and 3) they provided informed consent (**Table 1**).

The study was approved by the Ethics Committee of Okayama Health Foundation.

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Table 1. Clinical profiles of enrolled subjects.

	Men			Women		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Number of subjects	376			794		
Age	42.7 ± 13.2	20	74	40.6 ± 14.5	20	78
Height (cm)	170.3 ± 6.1	143.7	186.7	157.4 ± 5.3	140.5	172.9
Body weight (kg)	71.3 ± 11.7	42.0	120.3	54.4 ± 8.5	29.3	113.9
Body mass index (kg/m^2)	24.6 ± 3.6	14.6	41.8	22.0 ± 3.3	14.1	44.9
Abdominal circumference (cm)	85.3 ± 10.1	60.5	122.0	75.7 ± 9.8	55.1	120.0
Hip circumference (cm)	95.7 ± 8.4	74.5	193.4	92.0 ± 7.0	70.0	196.5
Systolic blood pressure (mmHg)	127.4 ± 13.8	94.0	191.0	114.7 ± 15.6	85.0	192.0
Diastolic blood pressure (mmHg)	75.9 ± 10.9	50.0	112.0	67.0 ± 10.9	40.0	111.0
Creatinine (mg/dl)	0.84 ± 0.12	0.51	1.34	0.62 ± 0.09	0.29	1.00
eGFR (ml/min/1.73 m^2)	83.2 ± 15.5	41.0	139.7	88.8 ± 18.2	42.5	172.9
Coffee consumption (cup/week)	9.5 ± 8.5	0	40	7.5 ± 7.9	0	50

2.2. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration [11].

2.3. Blood Pressure Measurements

Each participant's blood pressure was measured after resting at least 15 minutes in the sitting position.

2.4. Blood Sampling and Assays

The level of Cr was measured with an automated biochemical analyzer (model 7700; HITACHI, Tokyo, Japan) and Accuras Auto CRE (Shino-Test Corporation, Tokyo, Japan) at the Okayama Southern Institute of Health, Okayama Health Foundation. eGFR was calculated using the following equation: eGFR (ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$ × Age$^{-0.287}$ (for men) and eGFR (ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$× Age$^{-0.287}$ × 0.739 (for women) [9]. Reduced eGFR was defined as an eGFR < 60 ml/min/1.73 m^2.

2.5. Coffee Consumption

Subjects were asked how many cups of coffee per week. They were dichotomized into coffee consumers who drink one or more cups of coffee per day, and non-coffee consumers who seldom drink coffee. The way of drinking was not asked.

2.6. Statistical Analysis

Data are expressed as means ± standard deviation (SD) values. A comparison of parameters between the two groups was made using the unpaired *t*-test and covariance analysis. Simple correlation analysis was performed as well to test for the significance of the linear relationship among continuous variables: $p < 0.05$ was considered statistically significant.

3. RESULTS

The mean eGFR was 83.2 ± 15.5 ml/min/1.73 m^2 in men and 88.8 ± 18.2 ml/min/1.73 m^2 in women (**Table 1**). The mean coffee consumption was 9.5 ± 8.5 cups/week/person in men and 7.5 ± 7.9 cups/week/person. A diagnosis of reduced eGFR was made for 19 men (5.1%) and 27 women (3.4%). eGFR was negatively correlated with age in either sex (**Figure 1**).

We clarified the prevalence of subjects with coffee consumers among subjects who were not taking without medications (**Table 2**). Among the 1,170 Japanese subjects, 233 men (62.0%) and 400 women (50.4%) were coffee consumers (coffee consumption 1 cup/day ≥). The prevalence of coffee consumers was the highest in 50's in men and 70's in women.

In subjects not taking medications, we also compared eGFR levels between the groups with and without coffee

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consumers of the Japanese (**Table 3**). To avoid the influence of age, we used age as a covariate and compared eGFR between Japanese with and without coffee consumers using covariance analysis. The significant difference of eGFR was not noted between subjects with and without coffee consumers, even after adjusting for age.

4. DISCUSSION

We firstly evaluated the link between eGFR using newly developed in Japan and coffee consumption in Japanese without taking any medications. The difference of eGFR was not noted between subjects with and without coffee consumers.

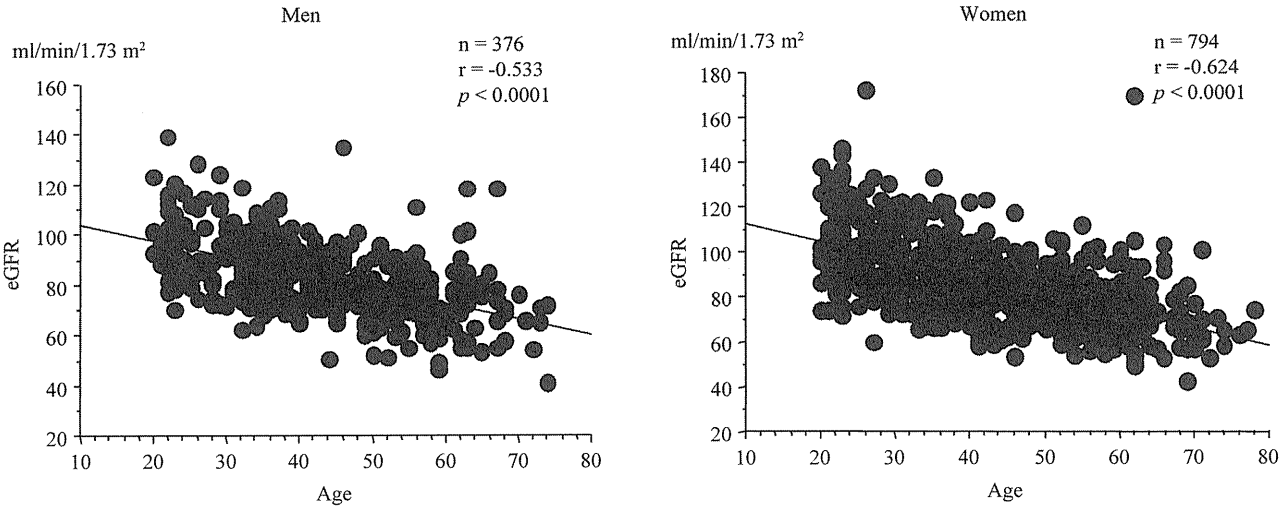

Figure 1. Simple correlation analysis between estimated glomerular filtration rate (eGFR) and age.

Table 2. Coffee consumption as classified by age groups.

	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70-	Total
Men							
Coffee consumption 1 cup/day <	44 (65.7)	37 (35.9)	32 (37.6)	16 (21.6)	12 (30.0)	2 (28.6)	143 (38.0)
Coffee consumption 1 cup/day ≥	23 (34.3)	66 (64.1)	53 (62.4)	58 (78.4)	28 (70.0)	5 (71.4)	233 (62.0)
Men							
Coffee consumption 1 cup/day <	206 (85.4)	73 (48.0)	37 (23.0)	45 (32.4)	29 (33.7)	4 (26.7)	394 (49.6)
Coffee consumption 1 cup/day ≥	35 (14.5)	79 (52.0)	124 (77.0)	94 (67.6)	57 (66.3)	11 (73.3)	400 (50.4)

Number of subjects (%).

Table 3. Comparison of eGFR between subjects as classified by coffee consumption.

	Coffee consumption 1 cup/day <	Coffee consumption 1 cup/day ≥	*p*	*p* (After adjusting for age)
Men				
Number of subjects	143	233		
Age	38.8 ± 13.7	45.1 ± 12.4	**<0.0001**	
eGFR (ml/min/1.73 m²)	86.5 ± 16.5	81.1 ± 14.4	**0.0009**	0.1375
Women				
Number of subjects	394	400		
Age	34.5 ± 14.3	46.6 ± 12.1	**<0.0001**	
eGFR (ml/min/1.73 m²)	94.1 ± 19.0	83.6 ± 15.9	**<0.0001**	0.2069

Mean ± SD.

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Iso *et al.* [2] reported that consumption of green tea, coffee, and total caffeine was associated with a risk for type 2 diabetes in 17,413 subjects with 5-year follow-up. Multivariable odds ratio for diabetes among participants who frequently drank coffee (3 cups of coffee per day ≥) was 0.58, respectively, compared with those who drank less than 1 cup per week. According to the link between habitual coffee consumption and eGFR in Japanese, Nakajima *et al.* [12] reported that eGFR in coffee consumers (n = 182) was significantly higher than that in non-coffee consumers (n = 160), which was not attenuated even after adjustment for age, sex and considerable factors. Kotani *et al.* [13] also reported that coffee drinkers had higher eGFR values than non-coffee drinkers in 114 Japanese. The difference remained significant, independently of clinical variables. However, in this study, we could not found the significant difference of eGFR between subjects with and without habitual coffee consumption. Compared the previous studies, the age enrolled in this study was younger. In addition, the age in subjects with habitual coffee consumption was significantly higher than that in subjects without in this study. Enrolled subjects in this study were taking no medications, suggesting apparently healthy subjects. Prolonged caffeine consumption has adverse effects on renal function in rats [6]. Therefore, the results may not be similar to previous reports.

Potential limitations remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, the 1170 subjects, all of whom wanted to change their lifestyle, underwent measurements for this study: they were therefore more health-conscious than the average person. Second, we could not clarify the mechanism the link between eGFR and coffee consumption. Third, the coffee consumption was reported to be 10.6 cups/week/person in 2008, and it is the highest between 40 and 59 (men: 13.5 cups/week/person, women: 14.2 cups/week/person) in Japanese by All Japan Coffee Association [1]. The coffee consumption was gradually increasing [1]. In this study, the mean of the coffee consumption was lower than that in the previous report. Further prospective studies are needed in Japanese subjects using the new Japanese criteria.

5. ACKNOWLEDGEMENTS

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ORIGINAL ARTICLE

Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study

Masaaki Nakayama · Toshinobu Sato · Hiroshi Sato · Yuji Yamaguchi · Katsuya Obara · Isao Kurihara · Kazuto Sato · Osamu Hotta · Jin Seino · Masahiro Miyata · Kazuhisa Takeuchi · Kenji Nakayama · Masato Matsushima · Tetsuya Otaka · Yasumichi Kinoshita · Yoshio Taguma · Sadayoshi Ito

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Abstract

Purpose Chronic kidney disease (CKD) can result from a wide variety of diseases, but whether clinical outcomes differ in the same CKD stages according to the underlying renal disease remains unclear. Clarification of this issue is important for stratifying risk of cardiovascular disease (CVD) and death in patients before dialysis.

Patients and methods The study comprised 2,692 patients recruited from 11 outpatient nephrology clinics, classified by underlying disease of primary renal disease (PRD) ($n = 1{,}306$), hypertensive nephropathy (HN) ($n = 458$), diabetic nephropathy (DN) ($n = 283$), or other nephropathies (ON) ($n = 645$). Risks of events such as ischemic heart disease, congestive heart failure, stroke, and all-cause mortality within 12 months were examined by logistic regression analysis in each group.

Result During the 12-months' observation from recruitment, 200 cases were lost to follow-up, and 113 cases were introduced to chronic dialysis therapy. A total of 69 CVD events occurred (stroke in 27 cases), and 24 patients died. In total, increased odds ratios (OR) for the events by CKD stage (cf. CKD1 + 2: unadjusted) were CKD3, 1.29 [95% confidence interval (CI), 0.70–2.17]; CKD4, 2.73 (1.55–4.83); and CKD5, 4.66 (2.63–8.23). Regarding events in respective groups, no significant differences were seen by CKD stage except for the group with HN, but significant differences were seen by underlying diseases (cf. PRD: adjusted for confounding factors, including estimated glomerular filtration rate): HN, 2.57 (1.09–6.04); DN, 12.21 (3.90–38.20); and ON, 4.14 (1.93–8.89).

Conclusion Risk of CVD and mortality due to CKD needs to be stratified according to the underlying renal diseases.

M. Nakayama (✉) · H. Sato · S. Ito
Tohoku University Graduate School of Medicine,
1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
e-mail: mnakayama@mail.tains.tohoku.ac.jp

T. Sato · O. Hotta · Y. Taguma
Sendai Shakaihoken Hospital, Sendai, Japan

Y. Yamaguchi
Japanese Red Cross Sendai Hospital, Sendai, Japan

K. Obara
Tohoku Kosai Hospital, Sendai, Japan

I. Kurihara
Tohoku Kosai Miyagino Hospital, Sendai, Japan

K. Sato · Y. Kinoshita
Japanese Red Cross Ishinomaki Hospital,
Ishinomaki, Japan

J. Seino
Sendai Medical Center, Sendai, Japan

M. Miyata
Osaki Citizen Hospital, Osaki, Japan

K. Takeuchi
Koujinkai Central Hemodialysis Clinic, Sendai, Japan

K. Nakayama
Sendai City Hospital, Sendai, Japan

M. Matsushima
The Jikei University School of Medicine, Tokyo, Japan

T. Otaka
Katta General Hospital, Shiroishi, Japan

Keywords Chronic kidney disease · Cardiovascular disease · Nephritis · Hypertension · Diabetic nephropathy

Introduction

Chronic kidney disease (CKD) [1] is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure, and all-cause mortality in the general population [2–8]. CKD is thus a major public health and economic burden. Screening for CKD is thus recommended around the world [1] using estimated glomerular filtration rate (eGFR) and testing for urinary proteinuria. Conversely, excess CVD morbidity and mortality by decreased kidney function has been shown in specific subpopulations with pre-existing heart disease, e.g., myocardial infarction (MI), congestive heart failure (CHF) [9, 10], hypertension [11], diabetes [12], and the elderly [13]. Accordingly, CKD resulting from renal disorders associated with those underlying pathological conditions may thus contribute strongly to excess CVD events [14, 15].

In primary as well as systemic renal diseases, patients show increased atherogenic factors such as hyperlipidemia and coagulopathy due to proteinuria, systemic inflammation-associated vasculitides, collagen or infectious diseases, and administration of steroids. All these factors could potentially increase CVD risks [16–19] Nevertheless, as CKD can result from a wide variety of diseases [1], whether clinical outcomes within the same CKD stages differ according to the underlying renal disease has not been clearly addressed. As the prevalence of chronic glomerulonephritis, such as immunoglobulin (Ig)A nephritis, is known to vary by ethnic background and geographical area, clarification of this issue is crucially important with respect to risk stratification of CVD and death in patients before dialysis. However, only a limited number of reports examined this issue [20, 21]. The study presented here, therefore, aimed to address this issue in a cohort of nephrology clinics.

Patients and methods

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of patient characteristics and outcomes for outpatient nephrology clinics in Miyagi prefecture (northeastern Japan). Eleven center hospitals, including one university hospital (Tohoku University Hospital), participated in the project, which covered almost the entire medical network of the area. Registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of Tohoku University School of Medicine and the respective attending hospitals. Registration was conducted from May 2006 to November 2008, and a total of 4,015 cases were registered. Among the original registered patients, the following were excluded from this analysis: 150 with lack of data on serum creatinine; 241 with unknown underlying renal diseases such as solitary microscopic hematuria ($n = 61$), or advanced renal failure or nephropathy of unknown origin ($n = 180$). Next, among patients with essential hypertension and eGFR > 60 ml/min, those who did not present positive proteinuria ($n = 836$) at registration or those lacking results of urinary testing ($n = 96$) were excluded. As a result, 2,692 patients were extracted as having complete CKD criteria [1] and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to the underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): (1) primary renal diseases (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including cases not proven by biopsy; (2) hypertensive nephropathy (HN), defined by preceding history of hypertension with absence of other possible disorders, including cases with biopsy findings of nephrosclerosis; (3) diabetic nephropathy (DN), defined by preceding history of diabetes accompanying nephropathy with absence of other possible renal disorders, including cases with biopsy findings of diabetic nephropathy or those who presenting nephropathy with diabetic retinopathy in the absence of other possible disorders; and (4) other nephropathies (ON), defined by other nephropathies not included in the other three groups: systemic or secondary renal disorders such as systemic vasculitis, collagen diseases, infectious diseases (e.g., hepatitis B or C), drugs, pregnancy, vascular disorders, urological disorders, and genetic disorders.

Primary outcomes of this survey included CVD such as angina pectoris (AP), acute AMI, CHF, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes by 12 months after registration were surveyed using hospital medical records, death certificates, and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (*International Classification of Disease*, 10th Revision: I00–I99), and the number of patients with AP or AMI included those who had received coronary stenting, angioplasty, or bypass operation or had definite clinical course of AMI. In cases with CHF, only those who needed

Table 1 Patients characteristics

	All	PRD	HN	DN	ON
Number	2,692	1,306	458	283	645
Age (years)[a]	60.0 ± 16.2	55.6 ± 16.6	70.2 ± 11.5	66.5 ± 12.6	58.6 ± 15.7
Gender (male)	1,439 (53.5%)	716 (54.8%)	261 (57.0%)	188 (66.4%)	274 (42.5%)
Body mass index[a]	23.5 ± 3.8	23.4 ± 3.8	24.2 ± 3.7	24.1 ± 3.8	23.0 ± 3.8
Blood pressure (mmHg)[a]					
Systolic	131 ± 16	129 ± 15	136 ± 17	137 ± 18	129 ± 16
Diastolic	77 ± 11	77 ± 10	77 ± 12	74 ± 12	77 ± 11
CKD stage					
Stage 1+2	1,088 (40.4%)	641 (49.1%)	81 (17.7%)	58 (20.4%)	308 (47.7%)
Stage 3	1,010 (37.5%)	467 (35.8%)	264 (57.6%)	80 (28.3%)	199 (30.9%)
Stage 4	361 (13.4%)	135 (10.3%)	72 (15.7%)	61 (21.6%)	93 (14.4%)
Stage 5	233 (8.7%)	63 (4.8%)	41 (9.0%)	84 (29.7%)	45 (7.0%)
Comobidities					
Cardiac disease	334 (12.4%)	98 (7.5%)	98 (21.4%)	70 (24.7%)	68 (10.5%)
Stroke	175 (6.5%)	46 (3.5%)	55 (12.0%)	36 (12.7%)	38 (5.9%)
Diabetes	743 (27.6%)	202 (15.5%)	144 (31.4%)	283 (100.0%)	114 (17.7%)
Hypertension	2,092 (77.7%)	950 (72.7%)	451 (98.5%)	253 (89.4%)	438 (67.9%)
Hyperlipidemia	1,165 (43.3%)	582 (44.6%)	193 (42.1%)	146 (51.6%)	244 (37.8%)
Pharmacotherapy					
ARB/ACEI	1,702 (62.2%)	810 (62.0%)	338 (73.8%)	216 (76.3%)	307 (52.4%)
Statin	936 (34.0%)	471 (36.1%)	149 (32.5%)	122 (43.1%)	194 (30.1%)
ESA	175 (34.0%)	46 (3.5%)	36 (7.9%)	62 (21.9%)	31 (4.8%)
Steroid	683 (34.0%)	430 (32.9%)	14 (3.1%)	6 (2.1%)	233 (36.1%)
Proteinuria	1,318 (50.0%)	617 (47.4%)	224 (51.9%)	221 (78.9%)	256 (41.1%)
Hemoglobin (g/dl)[a]	12.8 ± 2.1	13.2 ± 1.9	12.7 ± 2.1	11.6 ± 2.3	12.6 ± 2.0
Total cholesterol (mg/dl)[a]	198 ± 39	199 ± 36	191 ± 39	190 ± 41	203 ± 41
Smoker	428 (16.1%)	205 (15.8%)	70 (15.7%)	60 (21.6%)	93 (14.6%)
Biopsy	1,412 (62.8%)	1,055 (81.0%)	61 (21.4%)	48 (24.9%)	248 (53.1%)

CKD chronic kidney disease, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies, *ARB/ACEI* angiotensin receptor blocker/angiotensin converting enzyme inhibitor, *ESA* erythropoiesis stimulating agent, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies

[a] Mean ± standard deviation

admission for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke [22], and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Data collection

Serum creatinine was measured using the enzyme assay method. Kidney function was determined using the estimation formula for Japanese [23]. Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Positive macroalbuminuria was considered present for a dipstick result of + or more, corresponding to a urinary protein level of >30 mg/dl [24]. Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the patient in a seated position. Information on medications at baseline, as well as history of CVD, diabetes mellitus, hypertension, and hyperuricemia were obtained from the medical records or from results of blood examinations at registration. Patients receiving administration of lipid-lowering drugs or displaying serum cholesterol levels >220 mg/dl were considered to have hypercholesterolemia. Patients with fasting glucose levels >126 mg/dl or nonfasting glucose levels >200 mg/dl, or those who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and baseline kidney function as defined by CKD stage, positive for urinary proteinuria, and underlying renal diseases were examined using logistic regression analysis adjusted for age, gender, systolic blood pressure, body mass index (BMI), hemoglobin, serum albumin, presence of hyperlipidemia or diabetes, prescription of steroid, smoking habits, and history of CVD or stroke. Data are shown as means ± standard deviation (SD). Values of $p < 0.05$ were accepted as indicative of statistical significance. All statistical analyses were conducted using STATA version 10.0 software (Texas, USA).

Results

During the study period of 12 months observation, 200 cases were lost by changing to other medical services or stopping admission due to social reasons, and follow-up of 113 cases was stopped because of initiation of maintenance dialysis therapy. By 12 months, 69 cases of CVD events (27 cases of stroke) and 24 cases of all-cause death had been accumulated. Regarding primary events, significant increases in odds ratios (ORs) were seen by CKD stage under univariate analysis, but these trends disappeared under multivariate adjustment, and a significant lower risk was seen in stage 3 under multivariate analysis. In subanalysis excluding the ON group, there were significant increases in ORs by CKD stage under univariate analysis, but no significant changes were seen under multivariate analysis (Table 2).

Respective analyses by underlying renal disease are shown in Table 3. The same results were observed in the HN and DN groups but not in the PRD group.

ORs for primary events by underlying renal disease are shown in Table 4. Significant differences in ORs were seen in the HN, DN, and ON groups compared with the PRD group according to multivariate analysis.

Discussion

This study aimed to clarify the impact of differing underlying renal diseases on CVD events and death before initiation of dialysis treatment among 2,692 CKD outpatients from 11 nephrology clinics. By 12 months of follow-up, CKD stage was shown to be a significant risk factor for those events under univariate analysis but was not significant under multivariate analysis. However, the study confirmed significant differences in outcomes of CVD events and mortality according to underlying renal disease beyond CKD stage, even after adjusting for possible confounding factors, indicating a high-risk group of patients with HN or DN, and a low-risk group of patients with PRD. The exact mechanisms underlying increased risk of CVD in CKD have remained uncertain. Vascular dysfunctions developing in the uremic milieu may be involved with these pathologies. Associated factors could include fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, chronic inflammation, oxidative stress, and accumulation of uremic toxins [25–32]. Patients with established vasculopathy might reasonably be expected to undergo accelerated vascular damage with progression of CKD stage.

Table 2 Risk of primary endpoints by chronic kidney diseae (CKD) stage

Events				Univariate analysis		Multivariate analysis[a]	
CKD stage	CVD	Stroke	Death	OR	95% CI	OR	95% CI
All patients							
CKD 1+2	14	10	4	1.00		1.00	
CKD 3	22	6	6	1.29	0.70–2.17	0.54	0.30–0.98
CKD 4	15	6	7	2.73	1.55–4.83	0.79	0.38–1.66
CKD 5	18	5	7	4.66	2.63–8.23	0.95	0.39–2.28
Patients with PRD, HN, and DN							
CKD 1+2	10	3	1	1.00		1.00	
CKD 3	19	3	4	1.60	0.82–3.11	0.63	0.30–1.34
CKD 4	11	5	4	3.42	1.66–7.05	0.82	0.33–2.05
CKD 5	16	5	7	7.15	3.60–14.21	1.11	0.40–3.12

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON*, other nephropathies

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

Table 3 Risk of primary endpoints by chronic kidney disease (CKD) stage in respective underlying renal disease

Events				Univariate analysis		Multivariate analysis[a]	
CKD stage	CVD	Stroke	Death	OR	95% CI	OR	95% CI
Primary renal disease							
CKD 1+2	4	1	1	1.00		1.00	
CKD 3	5	1	1	1.29	0.41–4.04	0.32	0.07–1.41
CKD 4	1	0	1	0.72	0.09–6.02	0.11	0.00–1.38
CKD 5	0	0	1	1.54	0.18–13.03	0.14	0.00–2.98
Hypertensive nephropathy							
CKD 1+2	3	0	0	1.00		1.00	
CKD 3	8	2	1	1.16	0.31–4.30	0.21	0.03–1.32
CKD 4	5	3	1	3.70	0.95–14.27	0.32	0.04–2.37
CKD 5	4	2	3	4.48	1.05–19.03	0.20	0.01–2.18
Diabetic nephropathy							
CKD 1+2	3	2	0	1.00		1.00	
CKD 3	6	0	2	0.99	0.29–3.31	0.87	0.23–3.26
CKD 4	5	2	2	1.29	0.38–4.34	1.08	0.23–5.06
CKD 5	12	3	3	2.45	0.83–7.14	1.77	0.36–8.69
Other nephropathies							
CKD 1+2	4	7	3	1.00		1.00	
CKD 3	3	3	2	1.00	0.40–2.50	0.44	0.15–1.28
CKD 4	4	1	3	1.97	0.75–5.18	0.73	0.18–2.89
CKD 5	2	0	0	1.12	0.24–5.23	0.20	0.01–2.44

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

Table 4 Risk of primary endpoints by underlying renal disease

Underlying renal disease	Events			Multivariate analysis[a]	
	CVD	Stroke	Death	OR	95% CI
PRD	10	2	4	1.00	
HN	20	7	5	2.87	1.37–6.02
DN	26	7	7	11.88	4.58–30.83
ON	13	11	8	3.59	1.81–7.09

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

In this study cohort, all patients were recruited from nephrology clinics. This may have introduced a bias toward relatively better medical compliance in patients with modifiable factors, including uremic milieu and blood pressure. To note, the average blood pressure was well controlled as a whole in respective groups: 129/77 mmHg in PRD, 136/77 mmHg in HN, 137/74 mmHg in DN, and 129/77 mmHg in ON. On the other hand, patients with diabetes in this study may have been relatively resistant to conventional therapies, because most of them were originally introduced from diabetic clinics. Therefore, together with patient background, the findings of the study are not altogether surprising. Clinical outcomes of CVD and mortality differed significantly by underlying renal disease, such as relatively high CVD risk in DN and HN and relatively low risk in PRD. As hypertension, DM, and older age are all strong classic risk factors for predicting CVD in the general population, longstanding exposure to such pathological conditions may have resulted in increased CVD and mortality in HN and DN patients compared with patients with PRD with no clinical impact on CVD events of CKD staging.

As for the reasons for differing CVD outcomes in the group with PRD, several factors may have contributed. First, half of the patients showed IgA nephropathy in which glucocorticoid therapy does not increase the risk of CVD [33]. Blood pressure was also adequately controlled with angiotensin inhibitors, which may have improved patients'

clinical course, as shown in Japanese CKD patients [34]. In addition, we speculate that the uremic milieu for symptomatic CVD events may not be so clinically relevant in predialysis cases, instead starting to play a crucial role in the period of chronic dialysis, as has been indicated in pediatric patients in whom prevalent vasculopathy is not a dominant issue but who show high rates of CVD mortality and morbidity on dialysis [35, 36].

In this study, a significant lower risk was seen in stage 3 disease under the multivariate analysis compared with CDK stages 1+2 (Table 2). However, in subanalysis for groups excluding ON, no statistical difference was observed (Table 2), which implies the possible clinical significance of ON with stages 1+2 disease. The ON group consisted of various type of underlying diseases. In the ON group with stages 1+2, there were ten excess events in stroke or death, including patients with collagen diseases (four cases) and antineutrophil cytoplasmic autoantibody (ANCA)-related systemic vasculitis (one case). Therefore, we speculate that those types of underlying disorders might have increased the events in this group, and they predispose patients to high risks of death or vascular events independently of CKD stage. These results indicate that CKD staging cannot be simply applied to detect patients at high risk of CVD in the field of nephrology without taking into account differences in underlying renal disease, and those cases with prevalent hypertensive nephropathy or diabetic nephropathy should be the primary targets. Furthermore, as heart failure becomes dominant as CKD stage progresses, those cases should be managed with special attention to heart failure.

In this study, several clinical issues that might have biased the analytical results must be considered. First, angiotensin inhibitors were the leading agents prescribed to patients, whereas β-blockers, which benefit patients with heart failure, were the third-most prescribed agents. Second, hemoglobin levels among cases who developed heart failure were lower than those in their counterparts (data not shown), implying a need for anemia correction including induction of dialysis at an earlier time. Last, the study observation priod was relatively short—just 12 months—and therefore may not have been enough long to delineate the impact of CKD stage. This may, at least partly, account for the lack of significance of CKD stage for events by multivariate analysis. This should await further observations. In conclusion, risk of CVD and mortality due to CKD need to be stratified according to the underlying renal diseases.

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REVIEW ARTICLE

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Cardiorenal connection in chronic kidney disease

Sadayoshi Ito

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Abstract Chronic kidney disease (CKD), as defined by reduced glomerular filtration rate (<60 ml/min/1.73 m^2) and/or the presence of renal damage for >3 months, is a significant threat for public health in modern societies. Recent epidemiological studies have demonstrated that CKD is a significant risk for cardiovascular events independently of classical risk factors such as hypertension, dyslipidemia and diabetes. The mechanisms by which CKD increases the risk of cardiovascular events are currently under intensive investigation. Among various components of CKD, microalbuminuria is of particular interest, because it is a significant risk factor not only in diabetic and hypertensive subjects but also in the general population. Microalbuminuria is also closely associated with salt sensitivity of blood pressure, and the salt sensitivity is an independent risk factor for cardiovascular disease even in normotensive subjects. Several factors are likely to be involved in such associations, including the renin–angiotensin system (RAS), oxidative stress and inflammation. In addition, there may be more specific hemodynamic mechanisms in the kidney and other vital organs underlying these associations. This review describes 'the strain vessel hypothesis' as a possible mechanism for cerebrocardiorenal connections. In addition we discuss the significance of underlying diseases as cardiovascular risks of CKD as well as the role of RAS inhibition in the management of CKD patients.

S. Ito (✉)
Division of Nephrology, Endocrinology and Vascular Medicine,
Department of Medicine, Tohoku University School
of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai,
Miyagi 980-8574, Japan
e-mail: ishisho@med.tohoku.ac.jp

Keywords Microalbuminuria · Strain vessel · Cardiovascular disease · Pressure natriuresis

Introduction

Chronic kidney disease (CKD) is defined by reduced glomerular filtration rate (GFR) (<60 ml/min/1.73 m^2) and/or the presence of renal damage, such as microalbuminuria, for >3 months [1]. The incidence and prevalence of CKD are increasing worldwide, and CKD is a significant health problem associated with high morbidity, mortality and healthcare costs. In Japan, approximately 13 million patients have CKD, and this number is estimated to increase further in the future [2]. Patients with CKD are more likely to die than to progress to end-stage renal disease (ESRD), and cardiovascular disease (CVD) accounts for a large proportion of these deaths [3, 4]. The risk of cardiovascular events increases as the GFR becomes less and/or urinary albumin excretion becomes greater [5, 6]. The mechanism underlying the increased risk of cardiovascular events in patients with CKD has not been well-defined. It may be due to the fact that CKD patients often have multiple classical risk factors, such as hypertension, dyslipidemia and diabetes. However, even after adjustment for such factors, CKD is still significantly associated with high cardiovascular morbidities and mortalities. This has led to attention on non-classical risk factors, including decreased hemoglobin levels, microalbuminuria, increased inflammation and oxidative stress, and abnormalities in bone and mineral metabolism [1]. Despite intensive investigations, however, interrelations of these classical and non-classical risk factors are not well elucidated. In addition, the significance of each of these risk factors may differ depending on the original disease causing CKD.

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Cause of CKD and cardiovascular event

Epidemiological studies have established that both reduced GFR and increased urinary albumin excretion are related to heightened incidences of cardiovascular morbidity and mortality. However, the strength of each factor as cardiovascular risk may vary depending on the cause of renal impairments. For example, in immunoglobulin A (IgA) nephropathy proteinuria is a very strong and independent predictor of ESRD, but it does not seem to be associated with cardiovascular events. On the other hand, in patients with diabetes and/or hypertension, the presence of even a minute amount of albumin in the urine is related to high cardiovascular morbidity and mortality, and this risk increases as urinary albumin excretion becomes greater [7]. Thus, etiology of CKD, rather than absolute amount of urinary albumin excretion, may be important in order for albuminuria to impact on cardiovascular events. However, it is not well known whether the cause of renal dysfunction affects clinical outcomes of CKD patients, particularly in those receiving medical treatment.

We have recently commenced a longitudinal follow-up study of CKD patients treated by nephrologists in Miyagi prefecture, Japan (Miyagi Gonryo CKD Study), and a total of 2,692 CKD patients (not on dialysis) were available for analysis at 1 year [8]. In this cohort, the mean systolic and diastolic blood pressure (BP) was 131 ± 16 and 77 ± 11 mmHg, respectively, and the majority of patients received angiotensin receptor blockers (ARBs) and/or angiotensin-converting inhibitors (ACEI). It was observed that cardiovascular incidences and total mortality became higher as CKD stage elevated in univariate analysis (Fig. 1). However, in multivariate analysis (adjusted for age, gender, hemoglobin, positive for proteinuria, systolic BP, body mass index, presence of hyperlipidemia or diabetes, prescription of steroid, smoker, history of CVD or stroke), CKD stage had no influence on cardiovascular outcomes. On the other hand, underlying renal disease had a great impact on cardiovascular events and total mortality. Thus, in CKD patients well-treated by nephrologists, the underlying disease rather than CKD stage may be an important determinant of cardiovascular mortality and morbidity. In addition, appropriate care of the CKD patients may eliminate adverse influences of diminished GFR on cardiovascular morbidity and mortality, which were observed in many epidemiological studies in various populations. Finally, it should be mentioned that diabetic patients referred to our nephrology clinic had rather advanced nephropathy and atherosclerosis, which would explain the very high incidence of CVD.

Decreased GFR as cardiovascular risk

Numerous studies have shown that reduction of GFR to <60 ml/min/1.73 m^2 is associated with high cardiovascular mortality and morbidity, and the risk increases as decline of GFR becomes greater [5]. The mechanism underlying this increased risk associated with reduced GFR is probably related to the high incidence of classical and non-classical risk factors in these patients (Fig. 2). Both classical and non-classical risk factors cause renal damage, and renal dysfunction further aggravates classical risk

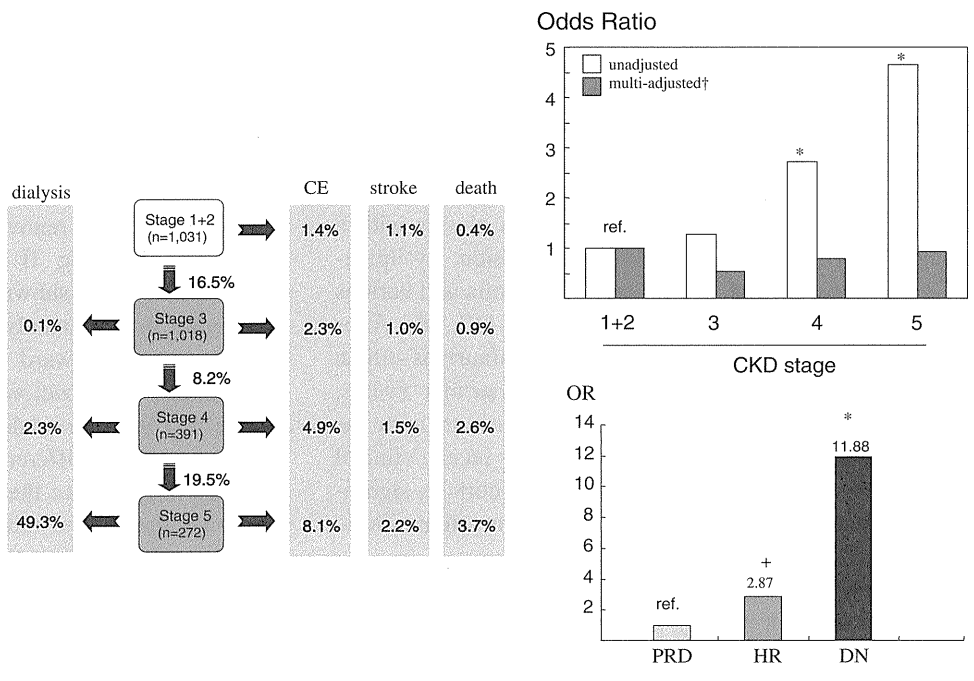

Fig. 1 Renal and cardiovascular outcomes at 1-year follow up of CKD patients enrolled in Miyagi Gonryo CKD study. **a** Renal and cardiovascular outcomes according to CKD stage. **b** Cardiovascular outcomes according to cause. *CE* cardiac event, *PRD* primary renal disease, *HR* hypertensive nephropathy, *DN* diabetic nephropathy. *Dagger* adjusted by age, sex, body mass index, hemoglobin, proteinuria, BP, dyslipidemia, diabetes mellitus, use of steroid, smoking, past history of cardiac disease or stroke