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

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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**).

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**).

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-

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

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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.

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

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.

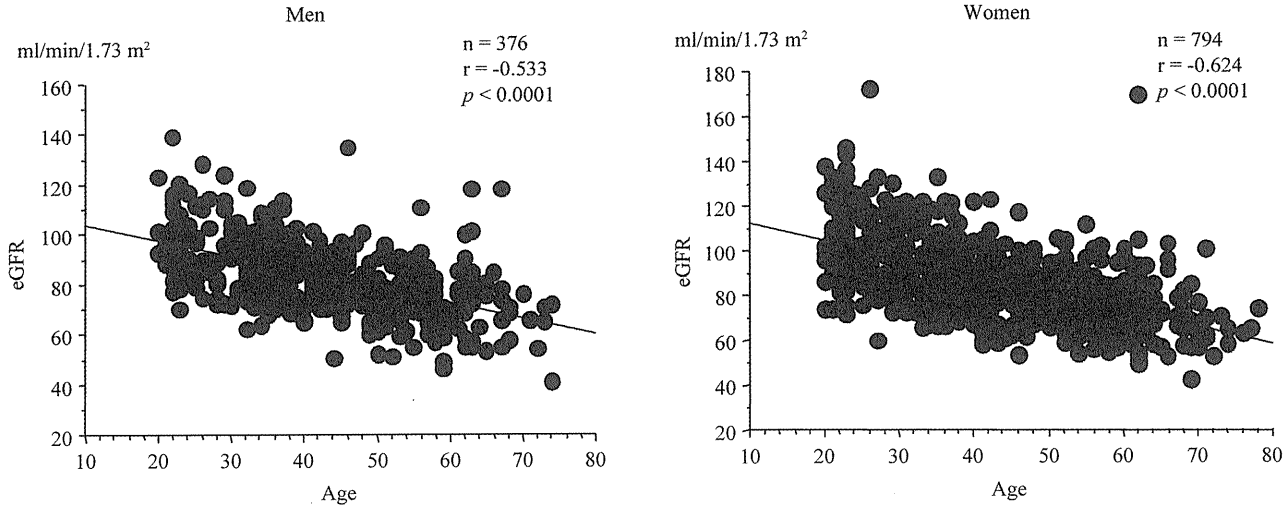

Figure 1. Simple correlation analysis between estimated glomerular filtration rate (eGFR) and age.

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.

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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REVIEW ARTICLE

The 36th IUPS Satellite Symposium:
The Kidney and Hypertension

Cardiorenal connection in chronic kidney disease

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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 cerebro-cardiorenal 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.

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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.

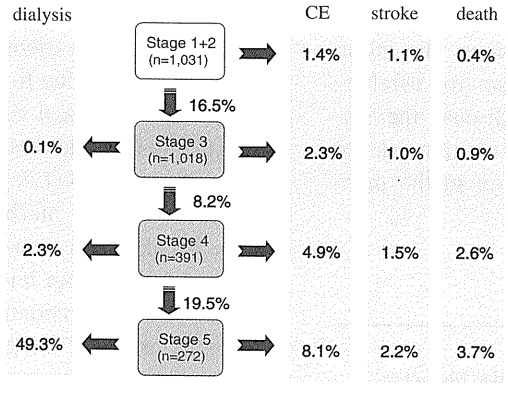
Cause of CKD and cardiovascular event

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



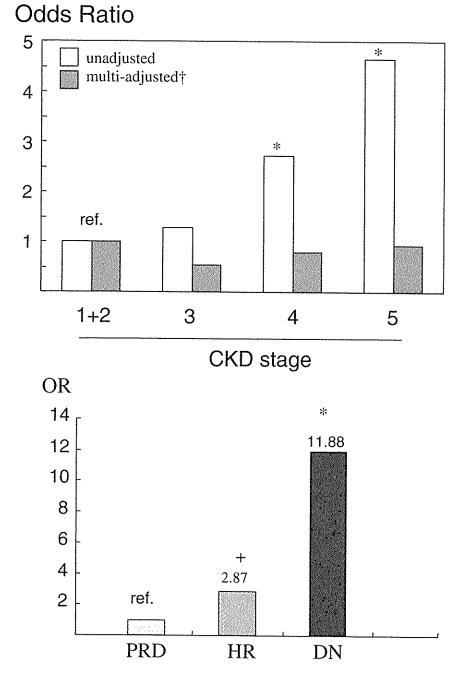


Fig. 1 Renal and cardiovascular outcomes at 1-year follow up of CKD patients enrolled in Miyagi Gonryo CKD study. **a** Renal and cardiovascular outcomes according to CKD stage. **b** Cardiovascular outcomes according to cause. *CE* cardiac event, *PRD* primary renal disease, *HR* hypertensive nephropathy, *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

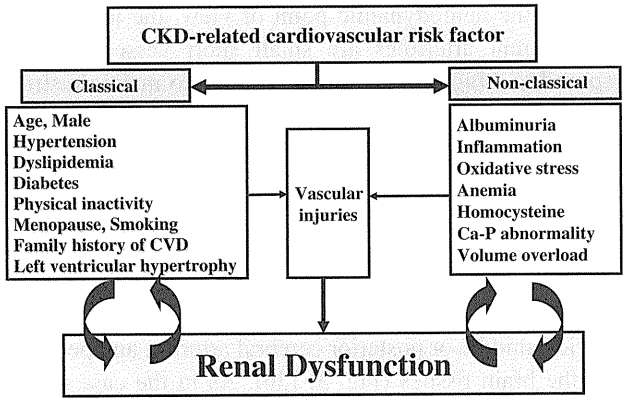


Fig. 2 Vicious cycle between vascular injuries and renal dysfunction

factors, as well as non-classical risk factors, thereby forming a vicious cycle. Both classical and non-classical risk factors are powerful accelerators of atherosclerosis. It has been shown that even moderate renal dysfunction is associated with enhanced oxidative stress and inflammation, which in turn accelerates atherosclerosis in the general circulation.

On the other hand, it has been shown that atherosclerotic vascular lesions are more prevalent in CKD patients than in non-CKD patients [9]. Thus, CKD reflects atherosclerosis, and CKD also accelerates atherosclerosis. This vicious cycle is present even in moderate reductions of GFR, and therefore, patients with CKD are more likely to die of CVD than to progress to ESRD.

Albuminuria as a cardiorenal risk

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 [10–14]. Studies have now shown that albuminuria even within the normal range is associated with a higher incidence and prevalence of stroke and CVD [15, 16]. Albuminuria has been shown to cluster with a number of risk factors including hypertension, dyslipidemia, renal dysfunction, hyperhomocysteinemia and various inflammatory and oxidative stress markers [17, 18]. After adjustment of these factors, however, albuminuria is still an independent predictor for adverse cardiovascular events, and this risk increases in a continuous fashion with the degree of albuminuria [16]. Furthermore, recent clinical trials have shown that reduction of albuminuria is significantly related to improved outcomes in albuminuric subjects [10, 19, 20].

The mechanisms of the association between albuminuria and CVD are still largely unknown and are a focus of intensive research and debate [21–23]. It has been suggested that albuminuria not only reflects glomerular damage, but is also a sensitive indicator of generalized endothelial dysfunction and capillary vasculopathy that leads to penetration of atherosclerotic lipoproteins into the arterial walls [24–26]. Studies showed that albuminuria was associated with endothelial dysfunction in the systemic circulation [26], but not all studies support this contention [27]. The issue of whether the endothelial dysfunction in the general circulation can be deduced from the presence of albuminuria is the subject of considerable debate, because glomerular endothelial cells are quite distinct from those of general circulation. Endothelial dysfunction of the glomerulus alone may not cause albuminuria unless it affects functions of basement membrane or podocytes [21].

Microalbuminuria results from glomerular injuries and/or reduced tubular reabsorption of filtered albumin. It is unlikely that all 2 million nephrons within the kidney contribute equally to such a miniscule amount of albumin leaking into urine. It is more probable that some nephrons are damaged, leaking a substantial amount of albumin, while the majority of others are not. The question is whether the nephron damage occurs randomly among all the nephrons or according to some principle. A random phenomenon would be difficult to explain such a close linkage between microalbuminuria and CVD, because there is no logical necessity. However, if there is a principle that causes nephron damage in certain subpopulations, and if the same principle applies to some mechanisms of CVD, then it would be able to explain the close linkage.

The strain vessel hypothesis

In hypertensive renal injury, considerable heterogeneities exist among different nephron populations [28–31]. Specifically, tissue injury is most obvious in the juxtamedullary region and outer medulla in spontaneously hypertensive rats (SHRs) [28], Dahl salt-sensitive hypertensive rats [29], renovascular hypertension [30] and angiotensin II (Ang II)-induced hypertension [31]. In addition, it has been shown that in SHRs glomerular lesions first appear predominantly in the juxtamedullary nephrons and then extend toward more superficial nephrons [28]. Such distinct localization of renal injuries and mode of progression may be related to anatomical and functional heterogeneities of different nephron populations.

Figure 3 illustrates the anatomical relationships of the renal vasculature and tubular segments. The juxtamedullary glomeruli are located deep in the cortex and their afferent arterioles arise from either the initial segment of the interlobular artery or directly from the arcuate artery. In more superficial nephrons, their glomerular afferent

arterioles branch off from the more distal segments of the interlobular arteries. Since glomerular capillary pressure is normally maintained at about 50 mmHg by autoregulation in all nephrons [32], the pressure gradient across the afferent arteriole would be greatest in the juxtamedullary nephron. In other words, the juxtamedullary afferent arteriole is exposed to unusually high pressure for a vessel of its size (about 20 μm), and is destined to maintain strong vascular tone in order to provide this large pressure gradient in a short distance between the large arcuate artery and the glomerulus. In contrast, in the superficial nephrons, a more gradual pressure reduction occurs along the greater length of vasculature including the entire interlobular artery and afferent arterioles. It is of note that the interlobular artery also participates in renal autoregulation [33, 34], and therefore the feeding pressure of superficial afferent arterioles is substantially lower than that of juxtamedullary afferent arterioles [33].

There are many diseases and mechanisms proposed to cause microalbuminuria [21]. As discussed above, however, regardless of the pathogenesis of microalbuminuria, the anatomical sites that are injured initially or more severely are the juxtamedullary afferent arterioles and glomeruli [29–31]. It would be reasonable to expect that in the early stages of hypertension, diabetes or aging, renal injury occurs predominantly in the juxtamedullary nephrons, while the majority of other nephrons remain relatively intact. This would be expected to result in only minimal increases of urinary albumin excretion. Indeed, we observed that in type 2 diabetic Otsuka Long-Evans Tokushima Fatty rats, podocyte injuries were evident only in the juxtamedullary, and not the superficial glomeruli, in the early stage of developing albuminuria (unpublished observation).

From the hemodynamic point of view, the juxtamedullary afferent arterioles are small short vessels that are exposed to a high pressure and destined to maintain strong vascular tone in order to provide a large pressure gradient in a short distance. We refer to these kinds of vessels as 'strain vessels' [35]. Thus, microalbuminuria may be an early marker of vascular damage of strain vessels within the body. Other 'strain vessels' exist most notably in the central nervous system where many perforating arteries arise directly from large high-pressure arteries such as anterior, middle or posterior cerebral arteries, and penetrate into the brain tissues (Fig. 3) [36]. As in the case of juxtamedullary afferent arterioles, these perforating arteries are exposed to high pressure and destined to maintain large pressure gradients from their parent arteries to brain tissue capillaries [37]. It is well known that the sites of hemorrhage or infarction in the brain are frequently the areas of blood supply governed by these perforating arteries [36, 38]. Thus, 'strain vessels injuries' may explain the link between vascular damage and microalbuminuria in the kidney and stoke.

There may be similar, albeit not the same, hemodynamic conditions existing in the coronary circulation [39]. It is well known that coronary blood flow depends primarily on diastolic and not on systolic BP. Coronary arteries arise directly from the aorta, and during the systolic phase there is little coronary blood flow because intramyocardial vessels are compressed due to myocardial contraction. This creates a unique situation that during the systolic phase the entire epicardial segments of coronary arteries, including small arteries just before their entering the myocardium, are exposed to very high pressure, because there is little outflow. Studies have shown that coronary arteries (particularly small-sized segments) exhibit myogenic responses

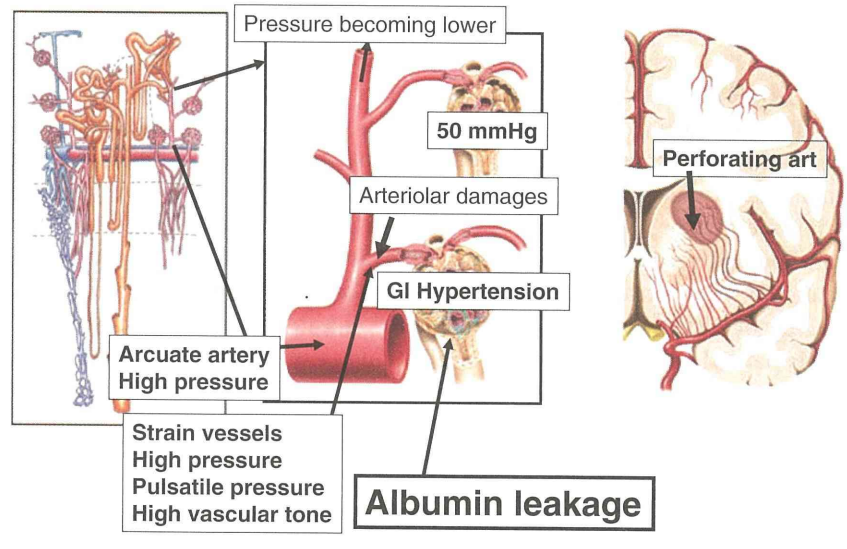


Fig. 3 Anatomical structures of the renal vasculatures and the tubular segments as well as perforating arteries in the central nervous system. Details are described in the text

[40], so that when intraluminal pressure is elevated, they would contract strongly in order to maintain vascular integrity. Therefore, although coronary arteries do not provide a pressure gradient, they would still be under high-pressure hemodynamic conditions with a strong vascular tone, which would be similar, though not the same, to those of strain vessels in the kidney and central nervous system.

According to our hypothesis, the importance of arterial stiffness for the association between cerebro-CVDs and albuminuria may be explained [41] by the fact that the strain vessels are directly influenced by the hemodynamics of large arteries. Unlike other small vessels in peripheral circulation where blood flow and pressure are rather constant, the strain vessels are exposed to pulsatile pressure and flow, and therefore stiffness of large arteries would have great impacts on the burden imposed on strain vessels [42, 43].

CKD components as cardiorenal risks

Figure 4 illustrates the relationship between CKD components and cardiorenal risks. As mentioned above, in such diseases as hypertension, diabetes and obesity, microalbuminuria would be a significant risk because it may reflect significant injuries of strain vessels. As endothelial and vascular damage become advanced, more and more glomeruli are injured, resulting in a substantial amount of albuminuria and reduced GFR. Therefore, microalbuminuria, which would indicate the presence of advanced glomerular as well as systemic vascular lesions, is a very strong risk of both renal and cardiovascular events in subjects with hypertension, diabetes and/or obesity.

On the other hand, macroalbuminuria does not seem to be a significant risk of CVD in primary glomerular diseases. Urine abnormality is the first sign of primary glomerular diseases, and its manifestation is often proteinuria (macroalbuminuria) rather than microalbuminuria. The degree of urine abnormalities reflects the degree of glomerular injuries. In addition, proteinuria induces tubulointerstitial damage within the kidney, thereby contributing to a decline of GFR. Indeed studies have established that the heavier the proteinuria, the faster the decline in renal function. Thus, in primary glomerular diseases, proteinuria is a significant renal risk, but it alone may not be a risk for CVD because strain vessels are not the primary sites of injuries.

Albuminuria and salt sensitivity of BP

One of the features of microalbuminuria is the close association with salt sensitivity of BP [44, 45], and this association is observed even in normotensive subjects [44]. Salt-sensitive hypertension is characterized by glomerular hypertension, microalbuminuria [46] and a higher mortality and morbidity of cardiovascular events [46, 47]. Interestingly, the association between microalbuminuria and CVD has been shown not only in diabetic or hypertensive populations but also in apparently healthy subjects [10–14].

There are many mechanisms involved in salt sensitivity of BP, and one of the mechanisms may be impaired pressure natriuresis. According to our strain vessel hypothesis, microalbuminuria indicates the existence of damage in juxtamedullary afferent arterioles and glomeruli, and therefore impairment of the downstream medullary

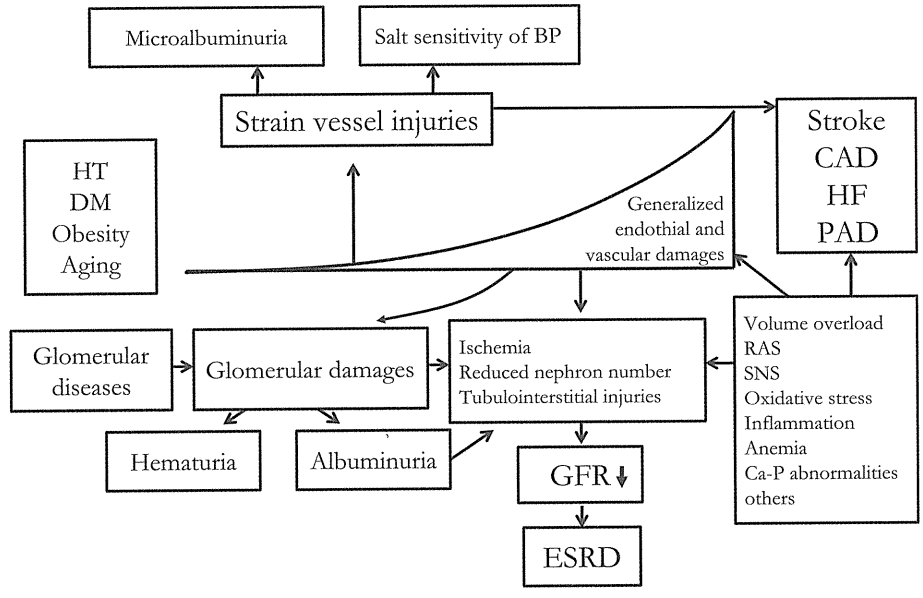


Fig. 4 Relationship among causes of CKD, endothelial and vascular injuries, urine abnormality, reduced GFR and cardiorenal events. *HT* hypertension, *DM* diabetes mellitus, *CAD* coronary artery disease, *HF* heart failure, *PAD* peripheral artery disease, *RAS* renin angiotensin system, *SNS* sympathetic nervous system

circulation. Since the medullary circulation plays a crucial role in the mechanisms of pressure natriuresis [48, 49], microalbuminuria may be related to impaired pressure natriuresis, and therefore, salt sensitivity of BP. In addition, in early stages of juxtamedullary glomerular injuries, there may be functional alterations in vasa recta. Namely, microalbuminuria could be caused by glomerular hypertension/hyperfiltration of juxtamedullary nephrons due to afferent arteriolar dysfunctions and impaired autoregulation. This hyperfiltration in the juxtamedullary glomeruli may cause constriction of descending vasa recta and thereby, functionally impair renal medullary circulation. It is of note that medullary thick ascending limb (mTAL) is anatomically located in the vicinity of the vasa recta that supply blood to the medulla. Studies have demonstrated the presence of tubulovascular cross talk in which nitric oxide or superoxide produced by the mTAL can diffuse into pericytes of descending vasa recta [50, 51]. By microperfusing mTAL segments in vitro, Abe et al. [52] demonstrated that an increase in sodium chloride concentration of the tubular perfusate stimulates superoxide anion production and decreases nitric oxide. Thus, hyperfiltration in juxtamedullary nephrons would increase sodium delivery to their own mTAL and stimulate superoxide production, which in turn may cause vasoconstriction of descending vasa recta (Fig. 5). Thus, our strain vessel hypothesis may explain the close interrelationships among microalbuminuria, salt sensitivity of BP and cerebro-cardiovascular mortality and morbidity. It should be noted, however, that other factors, such as the RAS and insulin sensitivity, also play a role in salt sensitivity of BP.

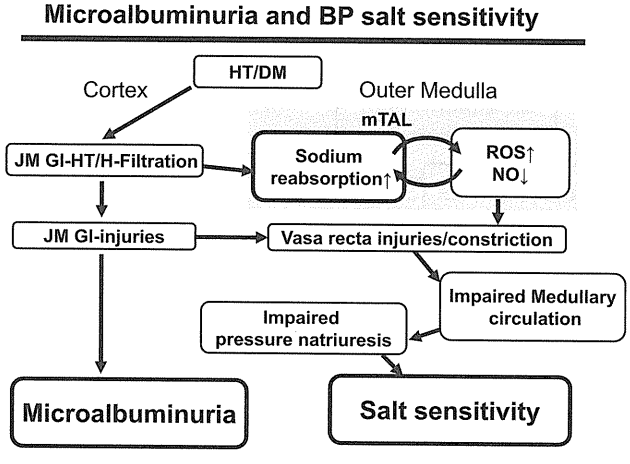


Fig. 5 Possible mechanism linking albuminuria and salt sensitivity of BP. Medullary blood flow is supplied via vasa recta, the downstream of the juxtamedullary glomerulus. In the phase of albuminuria, juxtamedullary glomeruli are injured, and therefore circulation of the downstream vasa recta is impaired. This in turn causes blunted pressure natriuresis and consequently an enhanced salt sensitivity of BP

Inhibitors of the RAS in the treatment of CKD

The inhibitors of the RAS have been shown to decrease both BP and urinary albumin excretion and to slow the progression of renal dysfunction significantly in diabetic and non-diabetic patients with CKD [53–56]. The renoprotective effects of RAS inhibitors are most prominent in patients with substantial amount of albuminuria [57]. Importantly, studies have reported that baseline as well as change in albuminuria during follow-up is closely associated with both renal outcome and cardiovascular mortality and morbidity [58–60]. Thus, it is recommended that strict BP control and reduction of albuminuria are the two important treatment goals for cardiorenal protection in CKD patients.

In contrast to the case for albuminuric patients, there is no convincing evidence that the benefits of RAS inhibitors extend to patients with less albuminuria [57]. Indeed, recent studies reported that a strong inhibition of the RAS may not be useful in certain populations. In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [61], a combination of high doses of ramipril and telmisartan did not offer any additional cardiovascular benefit beyond monotherapy with either drug alone, but it resulted in more adverse renal events of acute dialysis. In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSEND), treatment with a high dose of telmisartan, as compared with placebo, resulted in a significantly higher renal event rate, which was primarily driven by increased rate of doubling of serum creatinine [62]. Interestingly, subanalyses of these studies have clarified that those who experienced adverse renal events were normotensive, had normal renal function and normoalbuminuria [62, 63]. The underlying mechanism for this may be based on complex interplays among RAS, salt balance and renal function [64]. It is known that inhibition of RAS would lead to a greater chance of hypotension and acute renal failure under such conditions as acute illness, dehydration, sodium depletion with excessive use of diuretics or major surgical procedures. This may be the case particularly in normotensive subjects with normal renal function in whom the circulating RAS responds very sensitively to changes in sodium balance, thereby maintaining circulatory homeostasis. Furthermore, repetition of subtle renal insult, even if it was partially reversible, may have resulted in doubling of serum creatinine in such subjects who had high cardiovascular risks and may also have unrecognized intrarenal vascular lesions. In contrast to subjects with normal renal function, the circulating RAS is less responsive to changes in sodium balance in subjects with reduced renal function or microalbuminuria, because their BP is salt sensitive and body fluid volume is expanded under regular sodium intake.

Thus, the known benefits of RAS inhibition should be placed within the context of an expected risk of adverse effects. In CKD, modifying levels of albuminuria still remains an important strategy for renal and cardiovascular protection. However, for those at low renal risk and with low levels of albuminuria, RAS inhibition may not offer any renal benefit. It is advised that RAS inhibitors be used more judiciously, with dose titration and better monitoring of kidney function as well as BP. Although the RAS is deemed to cause vascular injuries independent of BP, we should keep in mind that the RAS is a critically important biological component in maintaining homeostasis of body fluid volume and BP.

An evolutionary point of view and perspectives

Why do we have such vulnerable structures as 'strain vessels' or the RAS that may cause organ damage? From the evolutionary point of view, we speculate that unique structures such as strain vessels in vital organs as well as neurohormonal systems such as the RAS would have been essential for creatures on the land in order to survive under their natural environments [35]. All creatures in their natural environment were constantly facing the danger of circulatory collapse. Given the generally difficult access to salt and a high risk of wound injuries, hypotension and hypoperfusion of vital organs were the principal challenges with which they had to cope, and the potent vasoconstrictor and sodium-retaining actions of RAS were indispensable for this purpose. In addition, in order to maintain the perfusion of the vital tissues such as brainstem, it was necessary to develop circulatory systems in which vessels branch off directly from the large arteries and deliver blood to the tissue. Taken together, the close link between microalbuminuria and CVD may be viewed as an inevitable consequence destined by evolution. In other words, while human beings enjoy the benefits of the many developments of the industrial revolution we have to keep in mind that our fate is still governed by the natural law of evolution. The 'strain vessel' hypothesis may explain why hypertension and diabetes, unforeseen in the concept of evolution, preferentially affect vital organs such as brain, heart and kidney.

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