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

Ethical considerations

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

Discussion

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

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

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

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

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

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

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

Progress of the study

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

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Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: The Hisayama Study

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Abstract

Background. Chronic kidney disease (CKD) is increasingly recognized as a leading public health issue. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities.

Methods. We performed three repeated cross-sectional surveys of residents aged ≥40 years in 1974 [2118 subjects (participation rate, 81.2%)], 1988 [2741 subjects (80.9%)] and 2002 [3297 subjects (77.6%)] in a Japanese community. We compared the prevalence of CKD [one or both of proteinuria and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2] and potential risk factors among the three surveys.

Results. The prevalence of CKD increased significantly with time in men (13.8% [95% confidence interval (95% CI), 11.4–16.2%] in 1974, 15.9% [95% CI, 13.6–18.2%] in 1988 and 22.1% [95% CI, 19.6–24.6%] in 2002; P for trend < 0.001), but not in women (14.3% [95% CI, 12.2–16.4%], 12.6% [95% CI, 10.9–14.3%] and 15.3% [95% CI, 13.4–17.2%]; P for trend = 0.97). The frequencies of individuals with CKD Stages 3–5 (eGFR < 60 mL/min/1.73 m^2) increased over the three decades in both sexes. Despite the widespread use of antihypertensive agents, the proportions of individuals with CKD who reached blood pressure of <130/80 mmHg were only 27.0% in men and 47.5% in women. The frequency of metabolic disorders including diabetes, hypercholesterolaemia and obesity increased over the three decades in both sexes.

Conclusions. The prevalence of CKD increased significantly in men, but not in women over the last three decades in a general Japanese population. Our findings support the requirement for a comprehensive treatment for hypertension and metabolic disorders to reduce the burden of CKD.

Keywords: chronic kidney disease; general population; hypertension; metabolic disorder; prevalence

Introduction

Chronic kidney disease (CKD), most commonly defined by a reduction in kidney function or the presence of proteinuria [1,2], is increasingly recognized as a leading public health issue. The number of patients with end-stage kidney disease has been expanding rapidly and is predicted to exceed 2 million worldwide by the year 2010 [3]. Furthermore, it has been established that CKD is a risk factor not only for progressive kidney failure, but also for cardiovascular morbidity and mortality [4–6].

Several cross-sectional studies have demonstrated that CKD affects 10–15% of the adult population in developed Western countries [7–9]. Recent epidemiological studies have suggested that CKD may be more prevalent in Asian countries than in developed Western countries [10,11]. Furthermore, it has been reported that the number of patients undergoing dialysis in Asian countries such as Malaysia and Japan has been increasing [12,13]. It is likely that the prevalence of CKD would increase over time as a consequence of the accumulation of risk factors such as hypertension, glucose intolerance, obesity and hypercholesterolaemia, probably owing to the westernization of the lifestyle in these Asian countries. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities to date. A better understanding of the past and current prevalence of CKD and its potential risk factors may provide useful information for the development of management strategies for CKD.

The Hisayama Study is a community-based cohort study that has been underway since 1961, with a goal of estimating the effects of the remarkable lifestyle changes on the burden of cardiovascular diseases in Japan [14–17]. The aim of the present study is to assess trends in the prevalence of CKD and its risk factors over the last three decades and to examine their relationships.

Subjects and methods

Study population

The town of Hisayama is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for 50 years and was approximately 8000 in 2008. The age and occupational distributions of the Hisayama population are almost identical to those of Japan as a whole. Full commu-

nity surveys of the residents have been repeated from the initiation of the study to date. The study design and characteristics of the subject population have been described in detail elsewhere [14–18]. Briefly, four study cohorts composed of Hisayama residents aged ≥40 years were established in 1961, 1974, 1988 and 2002. For this study, we used data from the cross-sectional surveys conducted at baseline in the latter three cohorts, which included available data on serum creatinine and proteinuria. The full community surveys were conducted as follows. In 1974, we invited all 2629 residents in that age group in the town registry to participate in the survey by the assistance of the town office, and of those, 2135 (participation rate, 81.2%) consented to participate in the health examination. After excluding 17 subjects for whom blood samples were unavailable, 2118 subjects (911 men, 1207 women) were enrolled in this study. In the same manner, 2741 subjects from 2742 participants (participation rate, 80.9%) in 1988 and 3297 subjects from 3298 participants (participation rate, 77.6%) in 2002 were enrolled in the study. A total of 3059 (38%) subjects participated in two or more of the three surveys.

Definition of CKD

Details of the measurement of risk factors in each survey were described previously [15,16,18,19]. Freshly voided urine samples were tested by the dipstick method in all surveys. Proteinuria was defined as 1+ or more. Serum creatinine was measured by the non-compensated Jaffé method in 1974 and 1988 and the enzymatic method in 2002. Serum samples were assayed using a Technicon autoanalyser (Technicon Instruments, Tarrytown, NY) in 1974, a TBA-80S autoanalyser (Toshiba Inc., Tokyo, Japan) in 1988 and an AU-800 autoanalyser (Olympus Corporation, Tokyo, Japan) in 2002. The difference between the serum creatinine levels by the Jaffé method and those by the enzymatic method was calibrated by using 98 serum samples standardized by CRC Corporation (Fukuoka, Japan). The range of creatinine levels in the samples was 0.5 to 15.2 mg/dl by the Jaffé method. The conversion equation was estimated by using a simple linear regression model. The correlation coefficient of this equation was 0.996. The Jaffé method value was converted to an enzymatic method value by using the following equation:

$$\text{Serum creatinine (enzymatic method [mg/dl])} = 0.9754 \times \text{serum creatinine(Jaff amethod[mg/dl])} - 0.2802.$$

The estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry–traceable creatinine-based four-variable Modification of Diet in Renal Disease (MDRD) Study equation with the Japanese Society of Nephrology Chronic Kidney Disease Initiatives coefficient of 0.741 [20]. eGFR was derived using the following equation:

$$\text{eGFR}\left(\text{mL/min/1.73 m}^2\right) = 0.741 \times 175 \times \text{serum creatinine(enzymatic method[mg/dl])}^{-1.154} \times \text{age(years)}^{-0.203} \times 0.742(\text{if female})$$

CKD was defined as either the presence of proteinuria or eGFR < 60 mL/min/1.73 m^2. The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [1]: Stage 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2 and the presence of proteinuria), Stage 3 (eGFR 30–59 mL/min/1.73 m^2) and Stage 4 or 5 (eGFR < 30 mL/min/1.73 m^2).

Risk factors

In each survey, blood pressures were measured three times in a sitting position after at least 5 min of rest, and the mean of the three measurements was used for the analysis. Hypertension was defined as a mean systolic blood pressure ≥140 mmHg or a mean diastolic blood pressure ≥90 mmHg or a current use of antihypertensive agents. Subjects with hypertension were classified as treated or untreated based on whether or not they were currently using antihypertensive agents. Diabetes was defined by fasting glucose concentrations ≥126 mg/dl (7.0 mmol/L) or postprandial glucose concentrations ≥200 mg/dl (11.1 mmol/L) in addition to medical history of diabetes in 1974 and by those methods and a 75-g oral glucose tolerance test in 1988 and 2002. Diabetes was regarded as treated when the subject was under therapy with insulin or hypoglycaemic agents in 1988 and 2002, but the designation of treated or untreated diabetes was not made in 1974 due to an absence of information on treatment status. Serum total cholesterol levels were determined by the Zurkowski method in 1974 and by the enzymatic method in 1988 and 2002. Hypercholesterolaemia was defined as serum total cholesterol ≥220 mg/dl (5.7 mmol/L) or current use of a lipid-modifying agent. Treated hypercholesterolaemia was defined as current use of lipid-modifying agents only in 2002 because information on anti-lipidaemic agents was not available in 1974 and 1988. Body height and weight were measured in light clothing without shoes, and the body mass index (in kilogrammes per square metre) was calculated. Obesity was defined as a body mass index ≥25 kg/m^2. Metabolic syndrome was defined by using criteria recommended in a joint interim statement of five major scientific organizations [21]. Information on medical history, medical treatment, alcohol intake and smoking habits was obtained through a standard questionnaire by trained interviewers. Alcohol intake and smoking habits were classified as either current habitual use or not.

Statistical analysis

The prevalences of CKD and each risk factor were adjusted for the age distribution of the world standard population in 1998 by using the direct method. The age-adjusted mean values of risk factors were calculated using the analysis of covariance method with age included as a continuous variable. Trends in the prevalence or mean values of each factor across survey years were assessed by fitting the logistic or linear regression model with evenly spaced numeric codes for the survey year, respectively. The age-adjusted relative risk (RR) and its 95% confidence interval (95% CI) for CKD were estimated by using Poisson regression analysis [22]. The SAS software package, release 9.2 (SAS Institute, Cary, NC), was used to perform all statistical analyses. A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

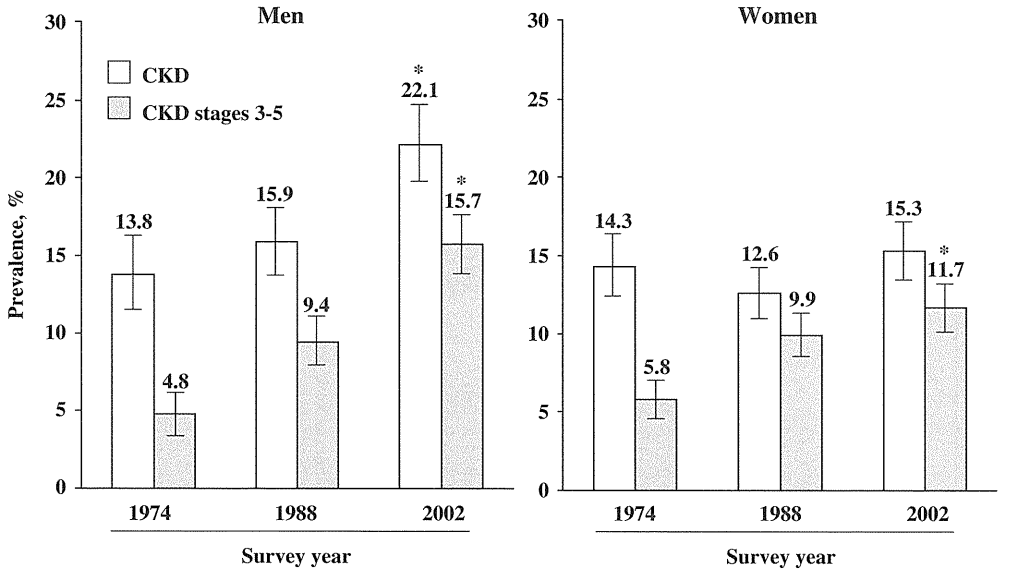
We compared the age-adjusted prevalence and mean values of risk factors among the three surveys by sex, as shown in Table 1. The prevalence of hypertension was constant in men, but decreased in women from 1974 to 2002. The prevalence of treated hypertension increased over time, whereas the prevalence of untreated hypertension decreased in both sexes. Consequently, mean blood pressure levels decreased over the last three decades. The frequencies of diabetes, hypercholesterolaemia, obesity, metabolic syndrome and alcohol intake increased with time, whereas the frequency of smoking habits decreased in both sexes. The prevalence of diabetes, especially untreated diabetes, increased with time in both sexes.

Figure 1 presents the age-adjusted prevalence of CKD in the three surveys by sex. The age-adjusted prevalence of CKD increased significantly with time in men (13.8% in 1974, 15.9% in 1988 and 22.1% in 2002; P for trend < 0.001), but not in women (14.3%, 12.6% and 15.3%, respectively; P for trend = 0.9). The prevalence of CKD Stages 3–5 increased 3-fold over time in men (4.8%, 9.4% and 15.7%; P for trend < 0.001) and doubled in women (5.8%, 9.9% and 11.7%; P for trend < 0.001). Conversely, the prevalence of CKD Stages 1–2 decreased to two-thirds in men (9.0%, 6.5% and 6.4%; P for trend = 0.02) and by half in women (8.5%, 2.7% and 3.4%; P for trend < 0.001). Similar trends in the prevalence of CKD across the three surveys were also observed in middle-aged and elderly populations in either sex (Figure 2). There was a comparable relationship for the prevalence of

Table 1. Age-adjusted prevalence and mean values of risk factors in 1974, 1988 and 2002 by sex

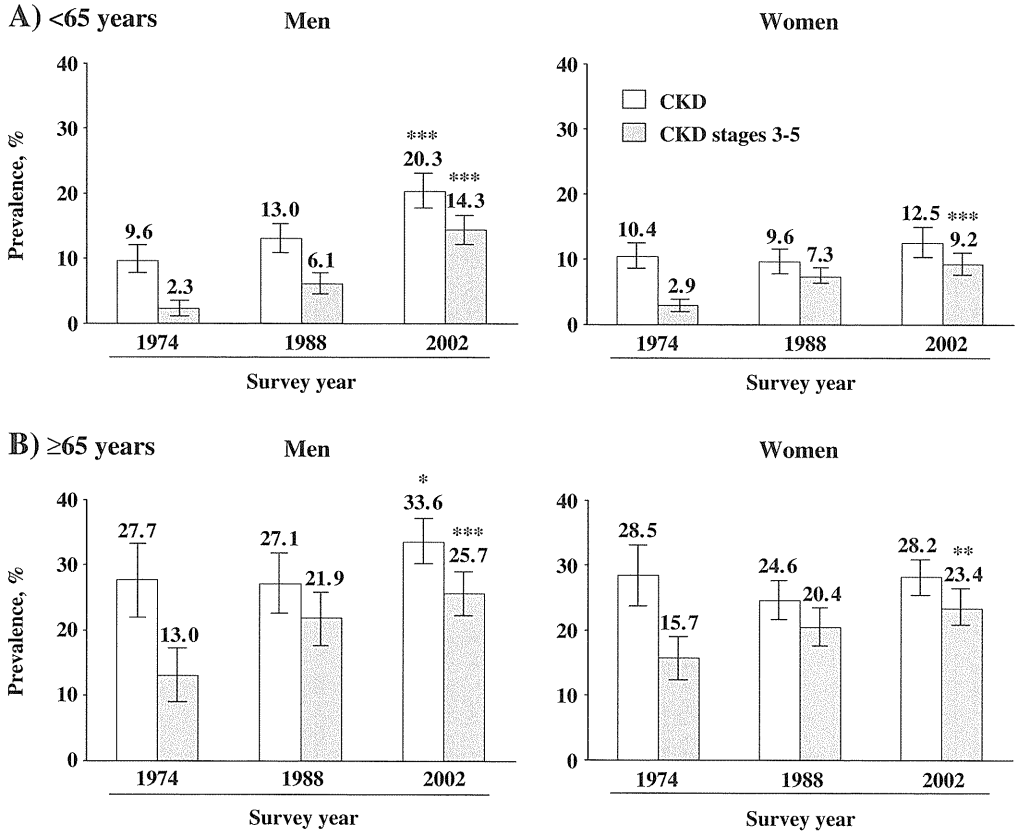
	Men				Women			
	1974 n = 911	1988 n = 1165	2002 n = 1414	P for trend	1974 n = 1207	1988 n = 1576	2002 n = 1883	P for trend
Age, years	56 ± 11	59 ± 12	61 ± 12	<0.001	57 ± 12	60 ± 12	62 ± 13	<0.001
Systolic blood pressure, mmHg	139 ± 21	136 ± 21	134 ± 21	<0.01	141 ± 21	134 ± 21	129 ± 21	<0.01
Diastolic blood pressure, mmHg	79 ± 12	81 ± 12	81 ± 12	<0.01	78 ± 12	76 ± 12	76 ± 12	<0.01
Hypertension, %	42.0 (39.0–46.0)	44.4 (40.6–48.2)	42.5 (39.0–46.0)	0.90	42.0 (38.4–45.6)	34.7 (31.9–37.5)	31.3 (28.9–33.7)	<0.001
Treated, %	9.2 (7.2–11.2)	13.8 (11.7–15.9)	19.4 (17.2–21.6)	<0.001	7.9 (6.4–9.4)	13.3 (11.6–15.0)	16.8 (15.1–18.5)	<0.001
Untreated, %	32.8 (29.1–36.5)	30.6 (27.4–33.8)	23.1 (20.4–25.8)	<0.001	34.1 (30.9–37.3)	21.3 (19.0–23.6)	14.5 (12.7–16.3)	<0.001
Diabetes mellitus, %	2.5 (1.5–3.5)	14.3 (12.1–16.5)	20.6 (18.2–23.0)	<0.001	2.0 (1.2–2.8)	9.0 (7.6–10.4)	11.5 (10.0–13.0)	<0.001
Treated, %	–	2.7 (1.8–3.6)	5.6 (4.4–6.8)	<0.001	–	2.6 (1.8–3.4)	2.8 (2.1–3.5)	0.23
Untreated, %		11.5 (9.5–13.5)	14.9 (12.8–17.0)	0.002		6.4 (5.2–7.6)	8.7 (7.3–10.1)	0.01
Hypercholesterolaemia, %	12.4 (10.1–14.7)	27.1 (24.0–30.2)	26.9 (23.9–29.9)	<0.001	20.3 (17.8–22.8)	41.4 (38.2–44.6)	41.0 (38.0–44.0)	<0.001
Treated, %	–	–	6.3 (5.0–7.6)	–	–	–	8.9 (7.7–10.1)	–
Untreated, %			20.6 (17.9–23.3)	–			32.1 (29.3–34.9)	–
Obesity, %	11.3 (9.1–13.5)	24.4 (21.4–27.4)	29.4 (26.2–32.6)	<0.001	21.3 (18.6–24.0)	23.9 (21.4–26.4)	23.8 (21.4–26.2)	0.004
Metabolic syndrome, %	–	8.1 (6.4–9.8)	13.4 (11.3–15.5)	<0.001	–	16.5 (14.5–18.5)	18.6 (16.7–20.5)	<0.01
Smoking habits, %	72.2 (66.6–77.8)	50.6 (46.4–54.8)	46.7 (42.6–50.8)	<0.001	10.2 (8.4–12.0)	6.9 (5.5–8.3)	8.6 (7.0–10.2)	0.002
Alcohol intake, %	63.6 (58.4–68.8)	61.9 (57.2–66.6)	71.2 (66.2–76.2)	<0.001	5.4 (4.1–6.7)	9.8 (8.1–11.5)	29.5 (26.6–32.4)	<0.001

Age is not age-adjusted. Values are means ± standard deviations or frequencies. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive agents. Diabetes mellitus was defined by fasting glucose concentrations ≥126 mg/dl (7.0 mmol/L) or postprandial glucose concentrations ≥200 mg/dl (11.1 mmol/L) in 1974 and by a 75-g oral glucose tolerance test in 1988 and 2002 in addition to a medical history of diabetes according to the recommendations of the American Diabetes Association. Hypercholesterolaemia was defined as serum total cholesterol ≥220 mg/dl (5.7 mmol/L) or current use of a lipid-modifying agent. Obesity was defined as body mass index ≥25 kg/m^2. Treated or untreated statuses were defined as the presence or absence of use of any medication for the treatment. Metabolic syndrome was defined by using criteria recommended in a joint interim statement of five major scientific organizations.



*P for trend < 0.01

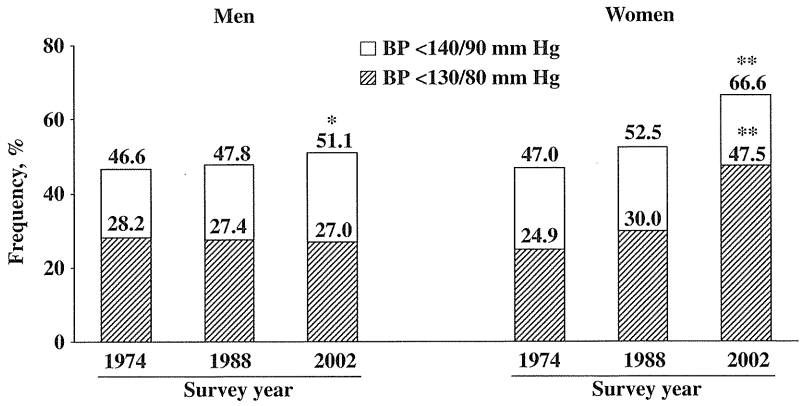
Fig. 1. Trends in the age-adjusted prevalence of CKD in 1974, 1988 and 2002 by sex.



*P for trend < 0.05, **P for trend < 0.01, ***P for trend 0.001

Fig. 2. Trends in the prevalence of CKD by age and sex.

CKD Stages 4–5, but the number of subjects with this stage of CKD was too small to assess reliably according to age or sex [eight subjects (0.4%) in 1974, seven subjects (0.3%) in 1988, 33 subjects (1.0%) in 2002 overall]. The number of subjects undergoing dialysis was zero in 1974, one in 1988 and 10 in 2002. The age-adjusted proportion of subjects with proteinuria did not change across the surveys in men (10.7% in 1974, 7.6% in 1988 and



*P for trend < 0.05, **P for trend < 0.001

Fig. 3. Age-adjusted frequencies of well-controlled blood pressure in subjects with CKD in 1974, 1988 and 2002 by sex.

Table 2. Age-adjusted prevalence of CKD according to hypertension status in 1974, 1988 and 2002 by sex

	Men				Women			
	1974	1988	2002	P for trend	1974	1988	2002	P for trend
Non-hypertension								
Prevalence (95% CI)[a], %	10.9 (7.6–14.2)	11.2 (8.5–13.9)	15.5 (12.7–18.3)		11.4 (8.4–14.4)	8.6 (6.6–10.6)	12.6 (10.5–14.7)	
RR (95% CI)[a]	1.00 (reference)	1.11 (0.76–1.61)	1.53 (1.09–2.17)	0.008	1.00 (reference)	0.79 (0.57–1.11)	1.13 (0.84–1.53)	0.20
Treated hypertension								
Prevalence (95% CI)[a], %	18.8 (10.7–26.9)	23.8 (16.7–30.9)	36.1 (23.7–48.5)		28.8 (15.8–41.8)	19.8 (13.3–26.3)	22.5 (10.8–34.2)	
RR (95% CI)[a]	1.00 (reference)	1.10 (0.70–1.77)	1.16 (0.78–1.81)	0.48	1.00 (reference)	0.79 (0.54–1.19)	0.72 (0.50–1.07)	0.11
Untreated hypertension								
Prevalence (95% CI)[a], %	16.6 (11.8–21.4)	17.5 (13.0–22.0)	28.8 (22.6–35.0)		15.8 (11.9–19.7)	16.7 (11.9–21.5)	19.8 (12.5–27.1)	
RR (95% CI)[a]	1.00 (reference)	1.00 (0.70–1.43)	1.65 (1.19–2.30)	0.001	1.00 (reference)	0.93 (0.69–1.27)	0.93 (0.68–1.28)	0.66

[a]Adjusted for age.

9.6% in 2002; P for trend = 0.65), but decreased significantly with time in women (10.2% in 1974, 3.8% in 1988 and 5.3% in 2002; P for trend < 0.001).

Next, we estimated the frequencies of well-controlled blood pressure in men and women with CKD in each of the three surveys (Figure 3). Among subjects with CKD, the proportion with blood pressure levels of <140/90 mmHg increased from 46.6% in 1974 to 51.1% in 2002 for men and from 47.0% to 66.6% for women, in parallel with the increment in the proportion of subjects taking antihypertensive agents. The frequency of blood pressure of <130/80 mmHg was <30% in men with CKD in all three surveys, whereas it increased from 24.9% in 1974 to 47.5% in 2002 in women. Among CKD subjects taking antihypertensive agents in 2002, 36.3% of men and 26.3% of women had a blood pressure level <140/90 mmHg, and only 11.1% and 12.8%, respectively, had a blood pressure level <130/80 mmHg. Table 2 shows the age-adjusted prevalence and RR of CKD by the status of hypertension treatment among the three surveys by sex. For men, the RR of presence of CKD increased with time in subjects with untreated hypertension (P for trend = 0.001), but not in subjects with treated hypertension (P for trend = 0.48). For women, there was no evidence of significant differences in the prevalence of CKD over time in any of the hypertension treatment statuses.

Finally, we assessed the relationship between metabolic syndrome and the risk of CKD in 1988 and 2002. Metabolic syndrome was associated with an increased risk of prevalent CKD in either sex (Figure 4). The strength of the relationship did not change over time for men (P for heterogeneity = 0.99), whereas it was attenuated significantly in 2002 compared with 1988 for women (P for heterogeneity = 0.01).

Discussion

In the present study, we demonstrated that the prevalence of CKD increased significantly in men, but not in women from the 1970s to the 2000s in a general Japanese population, whereas CKD Stages 3–5 increased progressively with time in both sexes. Importantly, more than half of

individuals with CKD did not reach the optimal target levels of blood pressure recommended by the current guidelines [23,24], despite an increment in the proportion of subjects taking antihypertensive agents over the last three decades. Furthermore, our findings implied that the recent increment in the number of subjects with metabolic disorders is linked to the increasing prevalence of CKD. These analyses, therefore, would seem to highlight the importance of the comprehensive management of metabolic disorders in addition to the strict control of blood pressure in order to reduce the burden of CKD in the general Japanese population.

The prevalences of CKD have been reported for several countries. The National Health and Nutrition Examination Surveys reported that the age-adjusted prevalence of CKD Stages 1–4 among subjects aged 20 years or older in the United States increased from 10.0% in 1988–1994 to 13.1% in 1999–2004 [8]. In Nord-Trondelag, Norway, the prevalence of CKD Stages 3–5 was 4.4% [9]. CKD may be more prevalent in Asian countries than in developed Western countries. A cross-sectional study conducted in 574 024 Japanese subjects over 20 years old demonstrated that the prevalence of CKD Stages 3–5 was 10.6 % in Japan [11]. Data from the screenings in Okinawa, Japan showed that the unadjusted prevalence of CKD Stages 3–5 among subjects aged 20 years or older increased between 1993 (10.4%) and 2003 (12.2%) in men, but decreased in women (19.5% in 1993, 17.4% in 2003), although the average serum creatinine levels increased in all age categories during this period in either sex [25]. An increasing trend in the prevalence of CKD in men was thus observed both in our study and Okinawa's study. The discrepancy observed in women between the two studies may have arisen from a self-selection bias caused by the low participation rate (<20%) in Okinawa's study, with subjects having an underlying disease (e.g. advanced kidney disease) being less likely to participate in the examination. Importantly, the prevalences of CKD in these studies were estimated on the basis of different eGFR equations, the direct comparison of which might be inappropriate. A nationwide examination will be needed to estimate the burden of CKD in Japan more reliably.

In the present study, the prevalence of metabolic disorders, such as diabetes, hypercholesterolaemia and obesity, was found to have increased dramatically over the last three decades, probably due to the westernization of lifestyle in Japan [26]. In the 2002 survey, diabetes was significantly associated with the likelihood of CKD for both sexes. Diabetes is an especially serious problem in the prevention strategy for CKD because it has been the leading cause of end-stage renal disease since 1998 in Japan [13]. Likewise, hypercholesterolaemia and obesity have been shown to be independent risk factors for CKD [27,28]. Our findings showed a jump in the prevalence of metabolic disorder from 1974 to 1988 ahead of the increment in the prevalence in CKD, possibly suggesting a causal association of metabolic disorder with the risk of CKD. In this study, furthermore, metabolic syndrome, which is defined as the accumulation of three or more risk factors such as elevated blood pressure, glucose intolerance, central obesity and dyslipidemia, was associated with an increased risk of CKD. Our previous longitudinal study has demonstrated that individuals with metabolic syndrome have 2.1-fold greater risk than those without it [29]. It has also been reported that clusters of multiple metabolic disorders tended to cause CKD in the several epidemiological studies [30,31]. Therefore, it is reasonable to suppose that the increasing prevalence of metabolic disorders has contributed to the increasing trend in CKD, especially CKD Stages 3–5, in our subjects.

Hypertension is well-established as a powerful risk factor for not only cardiovascular disease, but also CKD [32]. In this study, blood pressure levels significantly declined in both sexes over the last three decades, probably because of the widespread use of antihypertensive medication. Nevertheless, about 70% of men with CKD and 50% of women with CKD did not reach the optimal blood pressure levels of <130/80 mmHg even in the latest survey. Several clinical trials have demonstrated that blood pressure lowering was beneficial for the prevention of progressive kidney disease [33,34] and cardiovascular disease in individuals with CKD [35–38]. A recent meta-analysis of Japanese cohort studies also revealed that lower blood pressure level is linearly associated with a lower risk of cardiovascular disease and death in subjects with CKD [39]. These findings, therefore, suggest that blood pressure should be controlled more strictly in individuals with CKD, using the recommendations in the current guidelines [23,24].

Our study showed that the prevalence of CKD Stages 1–2 decreased over the last three decades in both sexes. Importantly, the frequency of women with CKD Stages 1–2 was halved over time, and therefore, the overall prevalence of CKD did not change. In the 2002 survey, blood pressure was well-controlled in women, compared with men (Table 1). It has been established that blood pressure-lowering therapy, particularly the use of renin–angiotensin system inhibitors, reduces the risk of the development of proteinuria and subsequent kidney dysfunction [40–45]. Furthermore, the relationship between metabolic syndrome and the likelihood of CKD for women tended to be attenuated from the 1988 survey to the 2002 survey, possibly due to early interventions, including lifestyle modification or medications against metabolic disorder. Thus, our findings imply that optimal management of blood pressure and metabolic disorder may reduce the prevalence of CKD in women in the next decade.

Several limitations of our study should be noted. First, it is well-known that eGFR values calculated using the MDRD study equation with a single measure of serum creatinine are not fully accurate. In addition, measurement of serum creatinine was not repeated after an interval of at least 3 months. Additionally, the values of serum creatinine were not calibrated using the values from the Cleveland Clinic, although they were calibrated across the three surveys. These matters may have caused some degree of misclassification of eGFR levels. Nevertheless, these limitations may have had little effect on our conclusions because the extent of misclassification of eGFR levels would be similar across the surveys. Second, the method for measuring serum cholesterol could not be calibrated across the surveys in this study. However, we believe that our findings with regard to the trend in the propor-

tion of hypercholesterolaemia over time are likely to be real because the proportion of obesity showed a similar pattern. Third, a 75-g oral glucose tolerance test was not performed in 1974. Thus, the prevalence of diabetes in 1974 was likely to be underestimated because the glucose tolerance test is a more sensitive method to diagnose diabetes. Fourth, the blood pressure levels were estimated with office blood pressure measurement, but not with home blood pressure monitoring, likely attenuating the accuracy of the information about blood pressure control. Fifth, we were unable to obtain information regarding the cause of CKD or the type of antihypertensive drugs, including renin–angiotensin system inhibitors. This information would have enabled a deeper understanding of our results. Finally, this is a cross-sectional study, and thus, the data are of limited use in inferring causality between risk factors and CKD.

Conclusion

In conclusion, the prevalence of CKD increased significantly in men, but not in women from the 1970s to the 2000s in a general Japanese population. Despite the popularization of antihypertensive medication, blood pressure was not sufficiently controlled over time to meet the optimal level recommended by the current guidelines for patients with CKD. Additionally, the increasing prevalence of metabolic disorders would be expected to play a role in the increasing trend in CKD. Our findings support the requirement for a comprehensive treatment for hypertension and metabolic disorders in order to reduce the burden of CKD.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Conflicts of interest statement. None declared.

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Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease

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Abstract

Background. There is substantial heterogeneity in literature regarding the epidemiology for chronic kidney disease (CKD) in different Asian populations. We aimed to assess the prevalence and risk factors of CKD in a multi-ethnic Asian population in Singapore.

Methods. We examined 4499 participants of Chinese, Malay and Indian ethnicity, aged 24–95 years, who

Association between urinary angiotensinogen levels and renal and cardiovascular prognoses in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Activation of the renin-angiotensin system (RAS) in the kidney plays an important role in renal function. The aim of this study was to investigate whether plasma and urinary angiotensinogen levels were associated with renal and cardiovascular prognosis in type 2 diabetic patients.

Materials and Methods: We measured plasma and urinary angiotensinogen levels in the observational follow-up cohort of 234 Japanese type 2 diabetic patients (144 with normoalbuminuria, 90 with albuminuria) enrolled between 1998 and 1999 and followed them up until the end of 2008. The associations of these markers with the annual decline in the estimated glomerular filtration rate (eGFR) and incidence of renal and cardiovascular composite endpoints (chronic hemodialysis, myocardial infarction, angina pectoris, stroke and cerebral hemorrhage) were evaluated.

Results: At baseline, urinary angiotensinogen levels correlated with urinary albumin-creatinine ratio, urinary β_2-microglobulin and inversely with eGFR. In contrast, plasma angiotensinogen levels correlated neither with these renal factors nor with urinary angiotensinogen levels. In the follow-up study (median duration: 9 years), urinary angiotensinogen, but not plasma angiotensinogen, correlated inversely with the annual change in eGFR ($r = -0.51$, $P < 0.001$). When patients were divided into four subgroups according to albuminuria and urinary angiotensinogen levels, patients with albuminuria and high urinary angiotensinogen levels showed a progressive decline of eGFR and a higher incidence of renal and cardiovascular composite endpoints.

Conclusions: These results suggest that the higher level of urinary angiotensinogen in type 2 diabetic patients with albuminuria is a high risk factor for worsening renal and cardiovascular complications. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00172.x, 2011)

KEY WORDS: Angiotensinogen, Diabetes mellitus, Glomerular filtration rate

INTRODUCTION

Diabetic nephropathy is a representative disorder of chronic kidney disease (CKD) and a leading cause of end-stage kidney disease (ESKD). This disorder is also associated with high morbidity and mortality of cardiovascular disease (CVD)[1–3]. Thus, prevention of development and progression of this disorder is of clinical importance to improve prognosis in diabetic patients.

Numerous clinical trials have documented that inhibition of the renin-angiotensin system (RAS) in diabetic patients can slow the progressive decrease in glomerular filtration rate (GFR) and reduce cardiovascular mortality and morbidity[4–6]. Based on clinical evidence, inhibition of the RAS is currently the first line treatment for diabetic nephropathy[7]. These results also support the concept that activation of RAS in diabetic patients is an important pathogenic mechanism of renal and cardiovascular complications[7]. However, despite the beneficial effects of RAS inhibition, all patients do not always show an improvement in the prognosis of these complications. Therefore, it is important to identify patients at higher risk of poor prognosis and a proper estimation of the status of intrarenal RAS activation may provide crucial information.

The kidney contains all components of the RAS pathway including the production of angiotensinogen[8]. Thus, the kidney can locally produce angiotensin II (AngII) by a mechanism independent of circulating AngII, known as the classical RAS pathway[8]. Intrarenally-produced AngII is reported to play an important role in renal hemodynamics and function as a paracrine factor[9].

We recently developed a direct method to quantify human plasma and urinary angiotensinogen levels using enzyme-linked

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immunosorbent assays (ELISA)[10]. Using this new method, we recently reported that urinary angiotensinogen may be a potential biomarker of the severity of CKD and intrarenal RAS status in hypertensive patients in the cross-sectional studies[11,12]. However, it is still unclear whether urinary and plasma angiotensinogen levels can be used to predict deterioration of renal function and the incidence of cardiovascular disease in a long longitudinal cohort. In the present study, we measured plasma and urinary angiotensinogen levels using our new ELISA method, in Japanese patients with type 2 diabetes who were enrolled in our observational follow-up study[2]. We then investigated whether these markers associate with renal and cardiovascular prognosis.

MATERIALS AND METHODS

Study Population and Samples

Japanese patients with type 2 diabetes mellitus were recruited from among participants who were registered in the Shiga Prospective Observational Follow-up Study between 1998 and 1999[2]. After obtaining written informed consent, each individual provided a spot urine sample and a fasting blood sample at baseline. The plasma and urine samples were kept at −80°C if not analyzed immediately. Based on the level of urinary albumin–creatinine ratio (UACR) at baseline, patients were classified as having normoalbuminuria (UACR < 30 mg/g Cr), microalbuminuria (30 ≤ UACR < 300 mg/g Cr), or overt proteinuria (UACR ≥ 300 mg/g Cr). Finally, 234 patients with normoalbuminuria (n = 144), microalbuminuria (n = 53) and overt proteinuria (n = 37) were enrolled and were followed up until the end of 2008 or the incidence of the renal and cardiovascular composite endpoints. In this study, patients with microalbuminuria and overt proteinuria were combined together into those with albuminuria (diabetic nephropathy). The participants underwent standardized clinical examination and biochemical tests annually, during the follow-up period. In this study, the values of HbA1c were presented in National Glycohemoglobin Standardization Program values according to the recommendations of the Japanese Diabetes Society[13]. The study protocol and informed consent procedure were approved by the Ethics Committee of Shiga University of Medical Science.

Measurement of Plasma and Urinary Angiotensinogen Levels

The concentrations of angiotensinogen in plasma and urine samples at baseline were measured with human angiotensinogen ELISA, as reported previously[10]. The sensitivity of this assay is >0.31 ng/mL. The intra- and inter-assay coefficients of variation were 4.4 and 4.3%, respectively. The urinary concentrations of creatinine were measured simultaneously by the enzymatic method. The urinary level of angiotensinogen was expressed in μg/g Cr.

Follow-up Evaluation

To evaluate deterioration of renal function, we assessed the annual decline in estimated GFR (eGFR). eGFR was calculated using the simplified prediction equation proposed by the Japanese Society of Nephrology[14]: eGFR (mL/min/1.73 m^2) = $194 \times [\text{age (years)}]^{-0.287} \times [\text{serum creatinine (mg/dL)}]^{-1.094} \times 0.739$ (for female). The serum concentration of creatinine was measured using the enzymatic method. The annual decline in eGFR over the course of the study was determined from the slope of the plot of all measurements of eGFR for each individual calculated by linear regression analysis and was expressed in mL/min/1.73 m^2/year.

We also investigated the incidence of the renal and cardiovascular composite endpoints, including myocardial infarction, angina pectoris, stroke and cerebral hemorrhage and initiation of chronic hemodialysis. Myocardial infarction was defined as a clinical presentation characterized by typical symptoms, electrocardiographic changes associated with an elevation of cardiac biomarkers and angiographic evidence of coronary thrombosis. Angina pectoris was defined as a history of typical chest pain and electrocardiographic changes compatible with ischemic heart disease or the detection of myocardial perfusion defects with exercise stress tests. Stroke and cerebral hemorrhage were defined as a persistent focal neurological symptom in which onset was sudden and was not due to trauma or a tumor and where the responsible lesion was detected by imaging studies.

Statistical Analysis

Data are expressed as mean ± SD or median (interquartile range). As compared between two groups, unpaired Student's t-test for continuous variables and chi-square test for categorical variables were applied. A comparison among three or more groups was performed by ANOVA with the Tukey-Kramer HSD test. Due to the skewed distribution, urinary angiotensinogen, UACR and urinary β_2-microglobrin (U-β_2MG) values were log-transformed before analysis. Pearson regression analysis was applied for analysis of the correlation between two variables, using logarithmic transformed values of non-normally distributed variables. A multivariate liner regression model was applied to evaluate the independency of factors that showed significant correlation in the univariate model. The cumulative incidences of renal and cardiovascular composite endpoints were estimated using Kaplan–Meier procedure and were compared by the log-rank test. The follow-up time was censored if any composite endpoint was observed or if the patient was unavailable for follow-up. Risk for renal and cardiovascular composite endpoint was evaluated by a Cox hazard regression model. A forward stepwise procedure was used to select explanatory variables with statistically significant effects on the time to the incidence of the endpoint. All analyses were performed by the SPSS software package (version 11; SPSS Inc., Chicago, IL, USA) and JMP for Windows (version 8.0.2; SAS Institute Inc, Cary, NC, USA). A two-sided P value <0.05 was considered statistically significant.

RESULTS

Baseline Clinical Characteristics

Table 1 lists the clinical characteristics of patients at baseline stratified by the stage of nephropathy. Gender, duration of diabetes, body mass index (BMI), HbA1c, systolic blood pressure

Table 1 | Clinical characteristics of the study subjects

	Normoalbuminuria	Albuminuria	*P*
Number	144	90	
Gender (male/female)	72/72	57/33	<0.05
Age (year)	60 ± 8	59 ± 9	n.s.
Duration of diabetes (year)	13 ± 8	16 ± 8	<0.01
Body mass index (kg/m^2)	23.1 ± 3.4	24.5 ± 3.7	<0.01
Waist to hip ratio	0.93 ± 0.08	0.95 ± 0.09	n.s.
HbA1c (%)	7.4 ± 0.8	7.9 ± 1.2	<0.01
Systolic blood pressure (mmHg)	135 ± 17	144 ± 19	<0.01
Diastolic blood pressure (mmHg)	77 ± 9	81 ± 10	<0.01
Taking RAS inhibitors (%)	16	31	<0.01
Past history of CVD (%)	13	20	n.s.
Total cholesterol (mg/dL)	213 ± 32	219 ± 37	n.s.
HDL-cholesterol (mg/dL)	60 ± 156	56 ± 15	n.s.
Triglycerides (mg/dL)	111 ± 32	135 ± 76	<0.05
Urinary ACR (mg/g Cr)	10 (7–15)	161 (61–672)	<0.05
Estimated GFR (mL/min/1.73 m^2)	81 ± 15	69 ± 26	<0.01
Urinary β_2-microglobulin (μg/g Cr)	114 (73–172)	188 (81–907)	<0.01

Data are mean ± SD for normally distributed continuous variables or median (25th–75th interquartiles) for skewed continuous variables. Albuminuria represents microalbuminuria and overt proteinuria. RAS, renin-angiotensin system; ACR, albumin-creatinine ratio; Cr, creatinine; GFR, glomerular filtration rate; CVD, cardiovascular disease.

(SBP), diastolic blood pressure (DBP), use of RAS inhibitors, triglyceride, UACR, eGFR and U-β_2MG were different between the normoalbuminuria and albuminuria groups.

Correlation Between Plasma Angiotensinogen Level and Various Parameters at Baseline

Plasma angiotensinogen levels were not different between two groups (normoalbuminuria: 24.7 ± 5.3, albuminuria: 24.1 ± 5.4 μg/mL). Univariate regression analysis showed weak correlations between plasma angiotensinogen levels and BMI, waist-hip ratio, SBP, total cholesterol, HDL-cholesterol and triglyceride, and no correlation with UACR, eGFR and U-β_2MG (Table 2). Plasma angiotensinogen levels were not different between patients treated with RAS inhibitors and those without them (24.4 ± 5.3 vs 24.6 ± 5.6 μg/mL, $P = 0.97$). Interestingly, plasma angiotensinogen levels were significantly higher in females than males (26.7 ± 5.3 vs 22.6 ± 4.6 μg/mL, $P < 0.001$). However, plasma angiotensinogen levels did not correlate with UACR, eGFR and U-β_2MG even when patients were analyzed separately according to gender.

Correlation Between Urinary Angiotensinogen Level and Various Parameters at Baseline

In contrast to plasma angiotensinogen, urinary angiotensinogen levels were higher in patients with albuminuria (62.0 μg/g Cr [interquartile range: 25.4–146.5]) than in those with normoalbuminuria (17.5 μg/g Cr [11.4–28.2], $P < 0.001$). Univariate regression analysis showed that urinary angiotensinogen levels correlated positively with UACR and U-β_2MG and inversely with eGFR (Table 2). Interestingly, there was no correlation between urinary angiotensinogen and plasma angiotensinogen ($r = 0.08$, $P = 0.21$). Urinary angiotensinogen levels were higher in patients treated with RAS inhibitors (38 μg/g Cr [19–133]) than those without (22 μg/g Cr [13–42], $P = 0.001$). However, this difference was probably due to the different prescription rate of RAS inhibitors in the two groups (normoalbuminuria: 16%, albuminuria: 32%). When urinary angiotensinogen levels were compared according to the stage of nephropathy, those in each stage were not different between patients treated with RAS inhibitors and those without. Unlike plasma angiotensinogen, the urinary angiotensinogen level in males was similar to that in females. Multiple regression analysis identified UACR and U-β_2MG as the independent and significant factors that correlated with urinary angiotensinogen levels.

Table 2 | Factors that correlated with plasma and urinary angiotensinogen levels in univariate analysis

Parameter	Plasma angiotensinogen		Urinary angiotensinogen	
	r	*P*	*r*	*P*
Age	−0.02	0.75	−0.07	0.31
Duration of diabetes	−0.10	0.11	0.24	<0.001
Body mass index	0.17	0.009	0.13	0.04
Waist to hip ratio	0.36	<0.001	0.10	0.15
HbA1c	0.10	0.14	0.26	<0.001
Systolic blood pressure	0.14	0.03	0.30	<0.001
Diastolic blood pressure	0.10	0.13	0.23	<0.001
Total cholesterol	0.35	<0.001	0.17	0.008
HDL-cholesterol	0.20	0.002	−0.12	0.06
Triglycerides	0.18	0.006	0.19	0.004
Urinary ACR	0.01	0.88	0.77	<0.001
Estimated GFR	0.04	0.59	−0.44	<0.001
Urinary β_2-microglobulin	−0.07	0.26	0.72	<0.001

Correlation was evaluated with the Pearson's correlation coefficient. The values of urinary angiotensinogen, urinary ACR and urinary β_2-microglobulin were log-transformed for the analysis because of their skewed distribution.
ACR, albumin-creatinine ratio; GFR, glomerular filtration rate.

Correlation Between Angiotensinogen Level and Annual Decline in eGFR

To explore the predictive role of plasma and urinary angiotensinogen levels for renal dysfunction, we investigated the correlation between each angiotensinogen and the annual change in eGFR during the follow-up period (median: 9 years, interquartile range: 6–10 years). As shown in Figure 1, urinary angiotensinogen, but not plasma angiotensinogen ($r = 0.00$, $P = 0.99$), correlated inversely with the annual change in eGFR ($r = -0.51$,

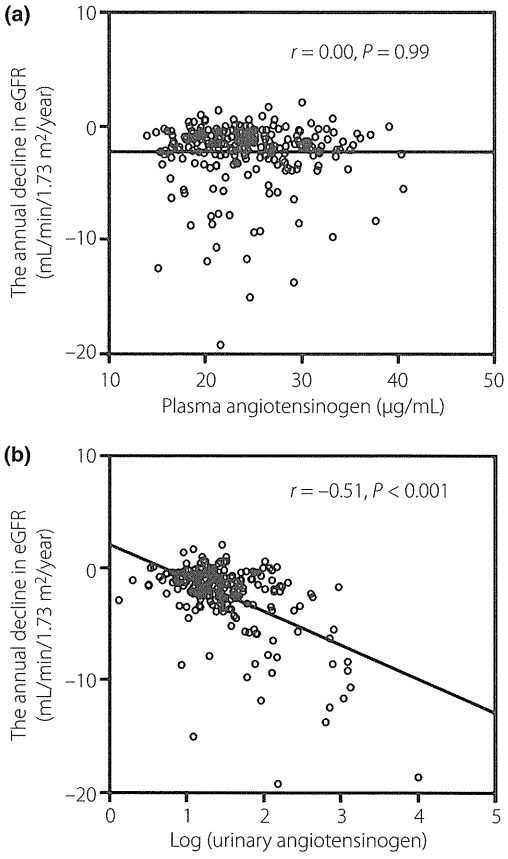

Figure 1 | Scatter diagram of the correlation between the annual decline in estimated glomerular filtration rate (eGFR) and (a) plasma angiotensinogen and (b) urinary angiotensinogen. Correlation was evaluated with the Pearson's correlation coefficient. Data are log-transformed values of urinary angiotensinogen.

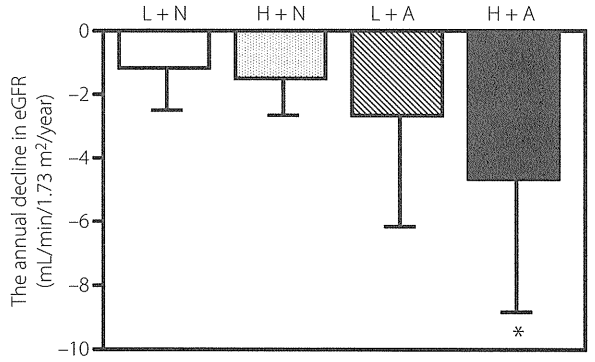

Figure 2 | Annual decline in estimated glomerular filtration rate (eGFR) during follow-up. Patients were divided into four groups using the median value of urinary angiotensinogen level (24.7 μg/g Cr) and the presence of albuminuria (>30 mg/g Cr). Patients with low levels of urinary angiotensinogen and normoalbuminuria (L + N, n = 97); patients with high levels of urinary angiotensinogen and normoalbuminuria (H + N, n = 47); patients with low levels of urinary angiotensinogen and albuminuria (L + A, n = 21) and patients with high levels of urinary angiotensinogen and albuminuria (H + A, n = 69). The respective annual decline in eGFR was: −1.2 ± 1.3, −1.4 ± 1.3, −2.7 ± 3.5 and −4.6 ± 4.2 mL/min/1.73 m^2/year. Data are mean ± SD. *P < 0.05 vs each other group (ANOVA with Tukey–Kramer HSD test).

P < 0.001). As other factors, the annual decline in eGFR correlated strongly with UACR (r = −0.65, P < 0.001) and correlated weakly with triglyceride (r = −0.28, P < 0.001), HDL-cholesterol (r = 0.15, P = 0.027), HbA1c (r = −0.22, P = 0.001), eGFR at baseline (r = 0.32, P < 0.001), BMI (r = −0.24, P < 0.001), SBP (r = −0.24, P < 0.001) and DBP (r = −0.23, P < 0.001).

Urinary Angiotensinogen and Renal Dysfunction in Patients with Albuminuria

Albuminuria is well known to be a risk factor for renal dysfunction and cardiovascular disease in patients with type 2 diabetes. Based on the strong correlation between urinary angiotensinogen and UACR, it was difficult to determine the specific role of each parameter in renal dysfunction. Therefore, to explore the clinical utility of measuring urinary angiotensiongen, we investigated the predictive effect of the combination of urinary angiotensinogen and albuminuria on deterioration of renal function. For this purpose, patients were divided into four groups according to the median value of urinary angiotensinogen levels (median cut-off values: 24.7 μg/g Cr) and the presence of albuminuria (>30 mg/g Cr). The eGFR at baseline (mL/min/1.73 m^2) was 80 ± 15 in those with low levels of urinary angiotensinogen and normoalbuminuria (L + N, n = 97), 84 ± 14 in those with high levels of urinary angiotensinogen and normoalbuminuria (H + N, n = 47), 82 ± 19 in those with low levels of urinary angiotensinogen and albuminuria (L + A, n = 21) and 66 ± 27 in patients with high levels of urinary angiotensinogen and albuminuria (H + A, n = 69). Among the four subgroups, the annual decline in eGFR during the follow-up was significantly greater in the H + A subgroup than other subgroups (P < 0.05 vs all other subgroup, Figure 2).

Urinary Angiotensinogen and Renal-Cardiovascular Outcomes in Patients with Albuminuria

Finally, we evaluated the association between urinary angiotensinogen at baseline and the incidence of renal and cardiovascular composite endpoints. A total of 58 patients experienced any of the composite endpoints (17 for chronic hemodialysis, 10 for myocardial infarction, 18 for angina pectoris, eight for stroke and five for cerebral hemorrhage). The incidence rate of this endpoint was higher in patients with high levels of urinary angiotensinogen than those with low levels of urinary angiotensinogen (36% vs 14%, χ^2 = 15.5, P < 0.001). Similarly, the incidence rate of this endpoint was higher in patients with albuminuria than those with normoalbuminuria (47% vs 11%, χ^2 = 37.6, P < 0.001). As shown in Figure 3, the cumulative incidence among the four subgroups was the highest in the H + A subgroup (log rank test: P < 0.001 for trend). Multivariate Cox proportional hazard regression model with the forward

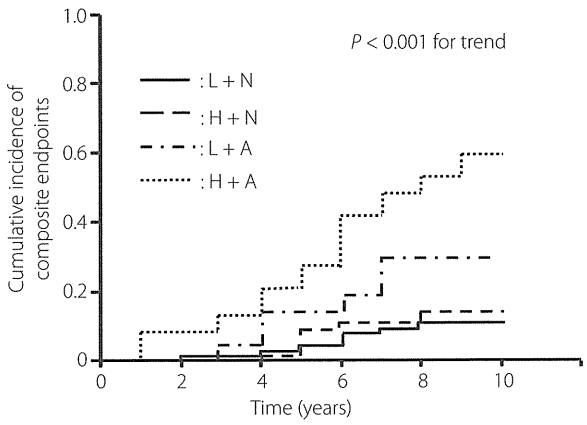

Figure 3 | Kaplan–Meier curves for cumulative incidence of renal and cardiovascular composite endpoints. Patients were divided into the four groups using the median value of urinary angiotensinogen level (24.7 μg/g Cr) and the presence of albuminuria (>30 mg/g Cr). Patients with low levels of urinary angiotensinogen and normoalbuminuria (L + N, $n = 97$); patients with high levels of urinary angiotensinogen and normoalbuminuria (H + N, $n = 47$); patients with low levels of urinary angiotensinogen and albuminuria (L + A, $n = 21$) and patients with high levels of urinary angiotensinogen and albuminuria (H + A, $n = 69$). Difference among the groups was tested by log rank test.

stepwise procedure identified four predictors of renal and cardiovascular outcomes: the combination of urinary angiotensinogen and albuminuria (adjusted odds ratio 4.5 [95% CI: 2.1–9.5] in H + A subgroup, 3.4 [1.2–9.3] in L + A subgroup and 1.6 [0.6–4.4] in H + N subgroup, 1.0 [reference] in L + N subgroup), age (1.04 [1.00–1.08]), eGFR at baseline (0.97 [0.96–0.98]) and past history of CVD (1.90 [1.06–3.41]).

DISCUSSION

In this study, analysis of baseline data showed that urinary angiotensinogen levels correlated with UACR and U-β_2MG and inversely with eGFR. In contrast, plasma angiotensinogen levels did not correlate with these factors or with urinary angiotensinogen levels. Furthermore, follow-up analysis indicated that patients with albuminuria and high levels of urinary angiotensinogen showed the progressive decline of renal function and the high incidence of renal-cardiovascular endpoints. These results suggest that the higher level of urinary angiotensinogen in type 2 diabetic patients with nephropathy is a high risk factor for worsening renal and cardiovascular complications.

In the present study, urinary angiotensinogen levels correlated closely with renal factors but did not correlate with plasma angiotensinogen levels. In contrast, plasma angiotensinogen levels correlated with various metabolic factors including BMI, waist-hip ratio and serum lipids, in agreement with the data of a previous report[15], but they did not correlate with renal factors. These results suggest that urinary and plasma angiotensinogen are produced by different sources and play different roles in renal function. Although angiotensinogen is produced and secreted by the liver, it is also produced in the kidney[9]. Previous studies have investigated whether circulating angiotensinogen is a source of urinary angiotensinogen. In hypertensive and normotensive rats infused human angiotensinogen, the circulating human angiotensinogen was not detectable in the urine, indicating limited glomerular permeability and/or tubular degradation of circulating angiotensinogen[16]. In the kidney under normal conditions, the expression of angiotensinogen is reported to localize in proximal tubular cells and angiotensinogen produced in proximal tubular cells is considered to be directly released into the renal tubular lumen[9]. Under diabetic conditions, the expression of angiotensinogen is reported to be enhanced in proximal tubular cells and to be also observed in mesangial cells[17,18]. Some human studies reported higher levels of urinary angiotensinogen in diabetic patients than in control subjects and patients with non-diabetic kidney diseases[11,19], whereas plasma angiotensinogen levels were similar in diabetic patients and control subjects[19]. Because the kidney contains all components of the RAS pathway, the enhanced expression of intrarenal angiotensinogen may lead to the intrarenal RAS activation. Thus, these results suggest that urinary angiotensinogen is produced locally in the kidney, but not from plasma, and its levels may associate with intrarenal RAS activation in diabetic patients.

In the present study, patients with high levels of urinary angiotensinogen, not plasma angiotensinogen, showed a greater decline in eGFR during the follow-up. A similar observation in patients with CKD documented the presence of higher urinary angiotensinogen levels in patients with low eGFR and patients with higher levels of urinary angiotensinogen showed increased risk of renal dysfunction during a mean follow-up period of 23 months[20]. Thus, urinary angiotensinogen is considered to be associated with the deterioration of renal function in patients with CKD including diabetic nephropathy.

Albuminuria is well known to be not only a predictor of progression to ESKD but also a risk factor for cardiovascular disease[1,2]. In this study, urinary angiotensinogen levels correlated closely with UACR as well as previous reports[12,21]. However, patients with albuminuria and higher levels of urinary angiotensinogen showed a progressive decline in eGFR and the high incidence of renal-cardiovascular endpoints than those with albuminuria and low levels of angiotensinogen. Thus, the increase of urinary angiotensinogen in patients with albuminuria may predict the patients at risk for worsening renal and cardiovascular complications.

What is the mechanism by which urinary angiotensinogen levels associate with worsening renal and cardiovascular complications? In this study, urinary angiotensinogen levels correlated with UACR and U-β_2MG. Transgenic mice overexpressing angiotensinogen in renal proximal tubular cells were reported to develop albuminuria, hypertension and renal injury[22]. The induction of diabetes with streptozotocin in these transgenic mice enhanced the aforementioned abnormal changes and induced apoptosis of renal proximal tubular cells[23]. Although diabetic nephropathy was traditionally considered to cause glomerular

damage primarily, it is now widely accepted that deterioration of renal function in diabetic patients correlates with the degree of tubulointerstitial fibrosis[24,25]. Thus, the enhanced expression of angiotensinogen in proximal tubular cells under diabetic conditions, which may correlate with urinary angiotensiongen levels, may cause the tubulointerstitial injury and, then, result in the decline in eGFR. Also the augmentation of urinary angiotensinogen is considered to lead to increased formation of AngII in the kidney[9]. Thus, the increase of urinary angiotensinogen may contribute to the development and progression of hypertension, which may associate with renal dysfunction and the incidence of cardiovascular disease. In the present study, urinary angiotenisinogen levels correlated with systolic and diastolic blood pressure as well as a previous report[12].

In this study, the data of clinical parameters including angiotensinogen were collected only at baseline. Thus, the time-dependent changes in these parameters during the follow-up were not evaluated. Also, the information regarding the use of RAS inhibitors during the follow-up period was not included in this study. Previous studies reported that RAS inhibitors were associated with reduction in urinary angiotensinogen levels[12,26]. In the present study, the levels of urinary angiotensinogen in patients treated with RAS inhibitors were not different from those without such treatment when data was analyzed separately according to the stage of nephropathy. In Japan, the prescription rate of RAS inhibitors in the past was much lower than that at present. Also, RAS inhibitors tended to be prescribed for patients who showed progression to the advanced stage of nephropathy or those at risk for cardiovascular disease. Thus, the present study does not provide conclusive data on the influence of RAS inhibitors on urinary angiotensinogen levels. Further studies are required to explore whether the reduction of urinary angiotensinogen level by any medication bring about improving renal and cardiovascular prognoses.

In conclusion, the present study demonstrated that urinary angiotensinogen levels correlated with progressive deterioration of renal function and the high incidence of renal-cardiovascular endpoints in patients with type 2 diabetes mellitus. These results suggest that higher levels of urinary angiotensinogen in patients with diabetic nephropathy are clinically useful to identify patients who are at high risk for worsening renal and cardiovascular complications. Also, the reduction of urinary angiotensinogen levels may be a new therapeutic index to prevent the worsening of renal and cardiovascular complications in diabetic patients with nephropathy.

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ORIGINAL ARTICLE

Significance of past history of renal failure for the detection of high-risk individuals for cardiovascular and end-stage renal disease: analysis of data from a nationwide health checkup

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Abstract
Background Clinical information regarding risk factors may be helpful in the detection of various diseases. This cross-sectional study examined the characteristics of subjects with past history of renal failure, and assessed whether this information would be useful for the efficient detection of high-risk individuals for chronic kidney disease (CKD) and cardiovascular disease (CVD) at health checkup.
Methods This study utilized data from a nationwide health checkup, "The Specific Health Check and Guidance in Japan," and data for 250,130 adult subjects were analyzed. Subjects with self-reported history of renal failure and receiving dialysis therapy were defined as having a history of renal failure.
Results Among total participants, there were 1,400 (0.6%) with a history of renal failure. The prevalence of a history of renal failure was higher in subjects with CKD than in those without CKD (1.5 vs. 0.3%, $P < 0.001$) and increased with progression of the stage of CKD (0.9–43.5%). Subjects with a history of renal failure had a reduced estimated glomerular filtration rate (44.6 ± 20.3 ml/min/1.73 m^2) and a higher prevalence of CKD (50.5%) and CVD (31.9%), compared with subjects with hypertension, diabetes or metabolic syndrome. Multivariate logistic regression analysis showed an independent association between a history of CVD and renal failure (odds ratio 3.68, 95% confidence interval 3.26–4.15), after adjustment for confounding factors.
Conclusions A history of renal failure was strongly associated with advanced CKD and CVD. Information regarding history of renal failure could be utilized to efficiently detect high-risk individuals at health checkup.

Keywords Chronic kidney disease · Epidemiology · Past history

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Introduction

Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (CVD) as well as end-stage renal disease; therefore, early detection and treatment of CKD is important [1]. Local health checks have been performed annually for the Japanese general population to facilitate the early detection of high-risk subjects for CKD and CVD. The main target of the recent health checkup "Specific Health Check and Guidance in Japan" was metabolic syndrome, which is associated with cardiovascular and kidney disease.

In mass screening programs, it is necessary from a cost-benefit perspective to efficiently detect high-risk subjects. Expensive investigations such as direct measurement of albuminuria may be acceptable in a high-risk population such as diabetic patients [2], but not in a low-risk population

such as the general population [3]. Therefore, for low-risk populations, it is desirable to reduce the number of subjects screened, by consideration of the characteristics of participants, including age and comorbidities [3]. For this purpose, previous studies have utilized information such as a family history of CKD [4, 5], and past history of hypertension and diabetes [6] for the detection of patients with CKD.

A question on past history of renal failure was included in the "Specific Health Check and Guidance in Japan" survey. This information on the history of renal failure may be useful for detecting subjects at high-risk of end-stage renal disease and CVD. Therefore, to clarify the characteristics of subjects with a history of renal failure, and to assess whether this information could be used for the efficient detection of high-risk individuals at health checkup, a cross-sectional study was conducted using data from the nationwide annual health check of the Japanese general population.

Methods

Study population

This study was part of the ongoing "Research on the Positioning of CKD in Specific Health Check and Guidance in Japan" program. The Specific Health Check and Guidance program is an annual health check in which all inhabitants over the age of 20 years who are covered by national insurance in Japan are invited to participate. Data from the nationwide database was obtained for 13 prefectures (Yamagata, Miyagi, Fukushima, Niigata, Tokyo, Kanagawa, Ibaraki, Osaka, Okayama, Kochi, Fukuoka, Miyazaki and Okinawa) that agreed with the study aims. In 2008 and 2009, data were collected on 278,017 men and 383,586 women (a total of 676,905 individuals, aged 20–101 years), who took part in the health checks. The study was approved by the institutional ethics committee.

Of the 676,905 participants, 426,775 were excluded from the present analysis because essential data, including information on proteinuria and serum creatinine levels, was incomplete. Therefore, data for 101,147 males and 148,983 females (a total of 250,130 individuals, aged 20–88 years) were used in the final statistical analyses. Among the 250,130 participants, there were 112,002 hypertensive subjects (44.8%), 27,820 subjects with metabolic syndrome (11.2%), 23,403 subjects with diabetes (9.4%), 138,535 subjects with dyslipidemia (55.4%) and 45,845 subjects with CKD (18.3%).

Measurements

Subjects used a self-report questionnaire to document their medical history, current medications, smoking habit (smoker or non-smoker) and alcohol intake (drinker or non-drinker). To assess their past history of renal failure, all participants were asked "Have you ever been told that you have renal failure or have you received dialysis therapy before?" If the answer was "yes," the subject was considered to have a past history of renal failure. The past history of renal failure mainly consists of past history of AKI and CKD stage 4 or 5. However, the patients on maintenance dialysis (stage 5D) were not included. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined using a standard sphygmomanometer or an automated device, with subjects in the sitting position after a sufficient period of rest. Hypertension was defined as a SBP $\geq$140 mmHg or a DBP $\geq$90 mmHg, or use of anti-hypertensive medication. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). For both men and women, obesity was defined as BMI $\geq$25.0 kg/m^2. Blood samples were obtained after overnight fasting. Plasma glucose levels were measured using the hexokinase enzymatic reference method. Subjects with diabetes were identified either by self-reported physical diagnosis or by a fasting plasma glucose concentration $\geq$126 mg/dl or a HbA1c value $\geq$6.5%. Triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations were measured by enzymatic methods. High-density lipoprotein cholesterol (HDL-C) concentrations were measured directly. Dyslipidemia was defined as triglyceride concentrations $\geq$150 mg/dl or LDL-C concentrations $\geq$140 mg/dl, or HDL-C concentrations $<$40 mg/dl or use of anti-lipidemic medication. Metabolic syndrome was defined according to the Japanese criteria for high waist circumference ($\geq$85 cm in men and $\geq$90 cm in women) plus any two of the following: (1) blood pressure $\geq$130/85 mmHg and/or use of anti-hypertensive medication; (2) fasting plasma glucose $\geq$110 mg/dl and/or use of anti-diabetic medication; and (3) triglyceride concentrations $\geq$150 mg/dl and/or HDL-C concentrations $<$40 mg/dl [7].

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early morning after overnight fasting. The results of the urinalysis were recorded as (−), trace, (1+), (2+) or (3+). Positivity for proteinuria was defined as (1+) or greater. Serum creatinine was measured using an enzymatic method, and the estimated glomerular filtration rate (eGFR) was calculated using the Japanese equation for eGFR [8]. We assumed the subjects with the presence of proteinuria and/or renal insufficiency (eGFR $<$60 ml/min/1.73 m^2) as having CKD. CKD was further categorized into five stages: stage 1, eGFR $\geq$90 ml/min/1.73 m^2 with proteinuria; stage 2, eGFR 60–89 with proteinuria; stage 3, eGFR 30-59; stage 4, eGFR 15–29; stage 5, eGFR $<$15 [9]. To investigate in detail the relationship between stage of CKD and history of