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.

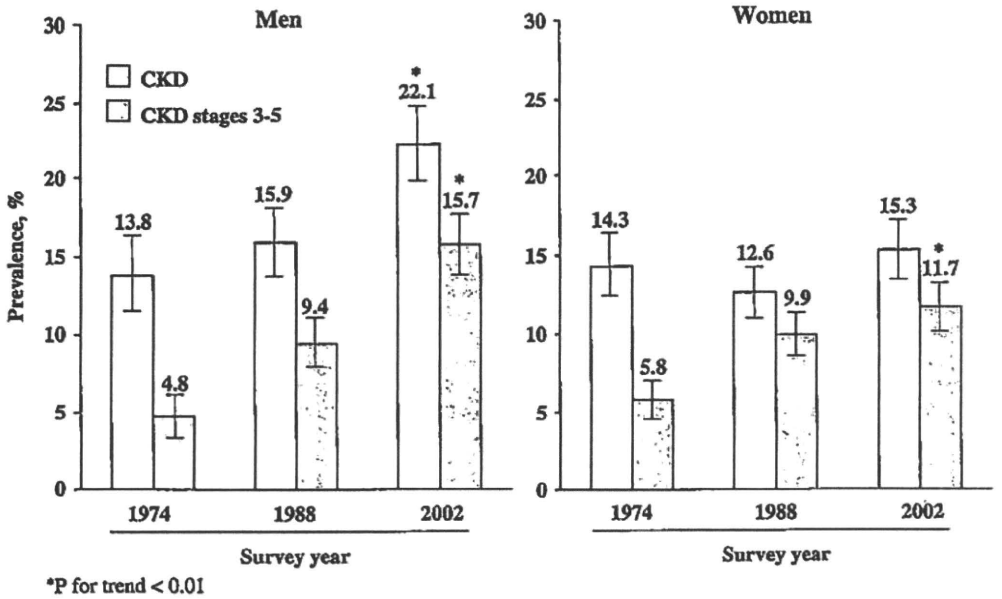


Fig. 1. Trends in the age-adjusted prevalence of CKD in 1974, 1988 and 2002 by sex.

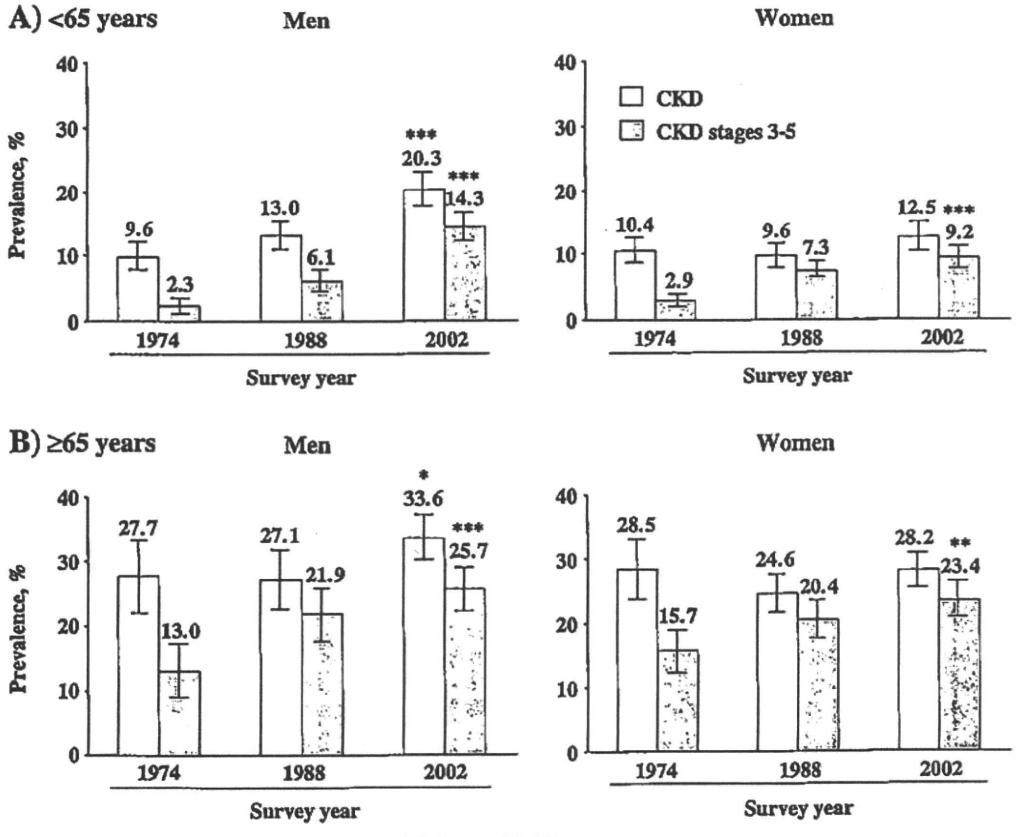
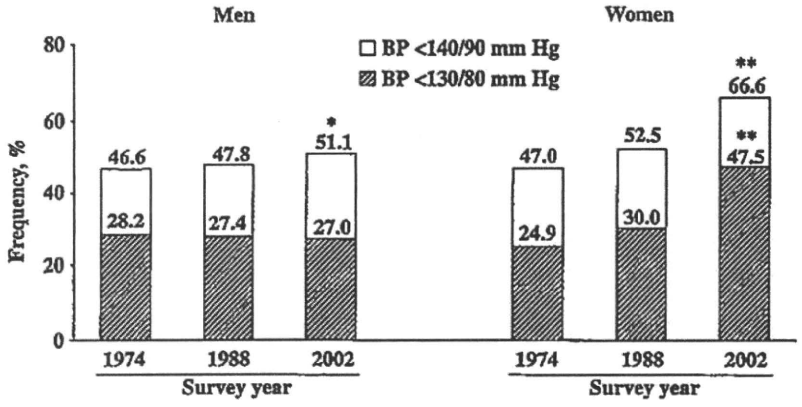


Fig. 2. Trends in the prevalence of CKD by age and sex.

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 of Kidney Function With Coronary Atherosclerosis and Calcification in Autopsy Samples From Japanese Elders: The Hisayama Study

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Background: Chronic kidney disease (CKD) is associated with increased risk of coronary heart disease. However, information regarding the histopathologic characteristics of coronary atherosclerosis in individuals with CKD is scarce. This study investigated the relationship between CKD and severity of coronary atherosclerosis in population-based autopsy samples.

Study Design: Cross-sectional study.

Setting & Participants: 126 individuals randomly selected from 844 consecutive population-based autopsy samples.

Predictor: Estimated glomerular filtration rate (eGFR) calculated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation.

Outcomes: Severity of atherosclerosis in 3 main coronary arteries, including atherosclerotic lesion types defined using the American Heart Association classification; stenosis rates; and coronary calcified lesions.

Measurements: The relationship between CKD and severity of coronary atherosclerosis was evaluated using generalized estimating equation methods.

Results: Frequencies of advanced atherosclerotic lesions increased gradually as eGFR decreased (33.6%, 41.7%, 52.3%, and 52.8% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; *P* for trend = 0.006). This relationship was substantially unchanged even after adjustment for potential confounding factors (ORs, 1.40 [95% CI, 0.76-2.55], 2.02 [95% CI, 0.99-4.15], and 3.02 [95% CI, 1.22-7.49] for eGFRs of 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively). Frequencies of calcified lesions of coronary arteries also increased gradually with lower eGFRs (*P* for trend = 0.02). Hypertension and diabetes were associated with increased risk of advanced coronary atherosclerosis and calcification of coronary arteries in individuals with decreased eGFR.

Limitations: Cross-sectional study, absence of data for proteinuria, and extremely high proportion of aged people.

Conclusions: The autopsy findings presented here suggest that CKD is associated significantly with severity of coronary atherosclerosis. Patients with CKD should be considered a high-risk population for advanced coronary atherosclerosis.

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INDEX WORDS: Chronic kidney disease; coronary atherosclerosis; population risk; coronary artery stenosis; glomerular filtration rate; coronary disease.

Editorial, p. 1

Chronic kidney disease (CKD) is a significant public health problem, affecting 10%-15% of the adult general population in developed countries.[1-3] CKD is associated with increased risks of cardiovascular disease and death.[4-7] A higher incidence rate of myocardial infarction and excessive cardiac mortality have been documented repeat-

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edly in patients with CKD.[6-10] Cardiac failure is more common in patients with advanced CKD, showing a prevalence of ~40%.[11]

Several autopsy-based studies have shown a higher prevalence of arteriosclerotic lesions in individuals with CKD than in those without CKD.[12-14] Furthermore, patients with end-stage renal disease show more advanced atherosclerotic lesions with calcification in coronary arteries than the general population.[14] However, these studies were conducted in hospital-based populations, which are prone to underlying disease. Additionally, there are few studies investigating the histopathologic findings of coronary arteries in individuals with moderate stage of CKD.

The Hisayama Study is a prospective population-based study of cardiovascular disease risk factors in Japanese people[15] and is characterized by autopsy verification of the cause of death in ~80% of those who died.[16,17] The present study assessed the relationship between decreased kidney function and severity of coronary atherosclerosis in population-based autopsy samples.

METHODS

Study Population

The Hisayama Study was established in 1961 in the town of Hisayama, a suburban community adjacent to Fukuoka City in a metropolitan area of Kyushu Island in southern Japan. The population of Hisayama is ~7,000 and has been stable for 40 years. Full community surveys of residents have been repeated since 1961.[18] From January 1988 to November 2005, a total of 1,162 residents of Hisayama died; of these, 844 underwent autopsy examination. Individuals without health examination data within 3 years before death were excluded. The remaining 482 individuals were classified into 4 categories based on estimated glomerular filtration rate (eGFR): ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2 (data from the most recent health examination). Eighteen individuals had an eGFR < 30 mL/min/1.73 m^2. The individuals included in this study were randomly selected using a computer-generated random number from each category of eGFR level after matching for age at death and sex in a 1:2 ratio against individuals in the <30-mL/min/1.73 m^2 category. A final total of 126 individuals (49 men, 77 women) were enrolled in this study (Fig 1). The median period from the last health examination to death was 1.0 years (quartile [Q] 1 to 3, 0.0-2.0).

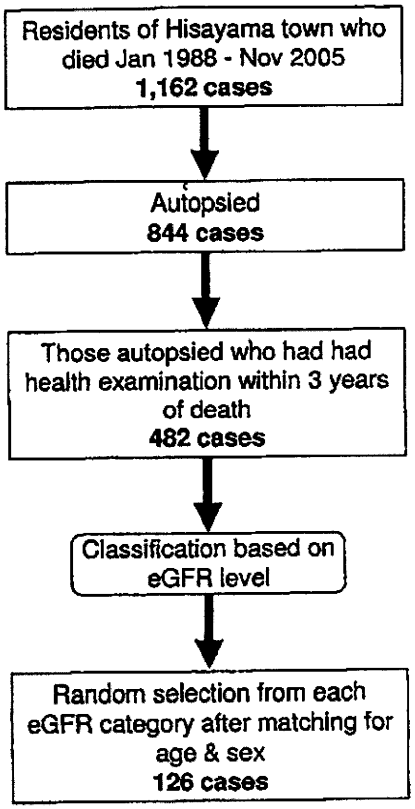

Figure 1. Flow diagram for study enrollment. Abbreviation: eGFR, estimated glomerular filtration rate.

Risk Factors

At each health examination, study participants undertook a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The completed questionnaire was checked by trained interviewers. Blood pressures were measured 3 times using a standard mercury sphygmomanometer at each examination, with mean values used for the analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive agents. Blood samples were collected after overnight fasting. Serum creatinine was measured using the Jaffé method. Hemoglobin A_{1c} was measured using high-performance liquid chromatography. Diabetes mellitus was diagnosed as hemoglobin A_{1c} level ≥ 6.0%. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined enzymatically. Dyslipidemia was defined as total cholesterol concentration ≥ 220 mg/dL, high-density lipoprotein cholesterol concentration ≤ 40 mg/dL, or triglyceride concentration ≥ 150 mg/dL.

Definition of CKD

eGFR was estimated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation,[19] and is given by the following equation (only 5 variables are shown because the multiplier for black race was not applicable to this population):

$$\text{eGFR (mL/min/1.73 m}^2) = 170 \times [\text{serum creatinine (mg/dL)}]^{-0.999}$$

$$\times [\text{age (years)}]^{-0.176} \times [\text{serum urea nitrogen (mg/dL)}]^{-0.170} \times [\text{serum albumin (g/dL)}]^{0.318} \times [0.762 \text{ if female}]$$

eGFR levels were classified into 4 categories: ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[20]

For sensitivity analyses, eGFR also was estimated using the 4-variable MDRD Study equation modified with the Japanese Society of Nephrology–Chronic Kidney Disease Initiative coefficient (ie, the JSN-CKDI equation)[21]:

$$\text{JSN-eGFR (mL/min/1.73 m}^2) = 0.808 \times 175 \times [\text{serum creatinine (enzymatic method [mg/dL])}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}]$$

where the value of serum creatinine measured using the Jaffé method was converted to values for the enzymatic method by subtracting 0.207 mg/dL.[22]

Coronary Artery Morphological Examination

Heart tissue obtained at autopsy was immersed in 10% buffered formaldehyde for at least 24 hours, making sure to include the 3 main coronary arteries. The right coronary artery (segment 1), left anterior descending coronary artery (segment 6), and left circumflex coronary artery (segment 11) were dissected free from the surface of the heart, cut perpendicular to the long axis at 3-mm intervals, and embedded in paraffin. The segment of the vessel showing the most severe stenosis was selected for histological examination, excluding areas near the branching site. Three blocks were excluded because the segments of the coronary arteries were not adequately defined. In total, 375 blocks were obtained and all blocks for each individual were cut into 3-μm-thick serial sections in 1 sequence (1 block provided insufficient sample to estimate the extent of arterial stenosis). Sections from each block were serially subjected to hematoxylin and eosin, elastica–van Gieson, and Masson trichrome staining. Histological examinations were made without reference to the associated clinical information by 2 independent pathologists (T. Nakano and S.S. in blinded assessments).

Estimation of Atherosclerotic Lesions

Atherosclerotic lesions found in each section were classified into 6 types in accordance with the definitions proposed by the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA)[23]: type I (initial lesion), intimal thickening with isolated foam cells; type II (fatty-streak lesion), intimal thickening with intracellular lipid accumulation; type III (intermediate lesion), type II changes and small extracellular lipid pools; type IV (atheroma), type II changes and core of extracellular lipid; type V (fibroatheroma), lipid core and fibrotic layer to lesions, or mainly calcified, or mainly fibrotic; and type VI (complicated lesion), disrupted lesion with hematoma or hemorrhage or thrombotic deposits. The AHA classification defines advanced atherosclerotic lesions as types IV-VI.[23] Lesion calcification was assessed on hematoxylin and eosin-stained paraffin sections from all specimens.

Morphometry of Luminal Stenosis in the Coronary Artery

All arteries were analyzed quantitatively for stenosis rate using computerized planimetry according to Taylor et al.[24] Morphometry was performed using National Institutes of Health (NIH) Image software (version 1.63; NIH, Bethesda, MD). Elastica-van Gieson–stained sections were magnified and digitized to measure the luminal internal and external elastic lamina perimeters. Arterial areas were calculated from diameter values derived from the measured arterial perimeter (area = πr^2) to avoid artifacts from vessel shape distortion during processing. Plaque areas were calculated as the differences between internal elastic lamina and luminal area measurements. Percentage luminal stenosis was calculated as plaque area/internal elastic lamina area × 100.[24]

Statistical Analysis

The SAS software package for Windows, version 9.1 (SAS Institute Inc, Cary, NC) was used to perform statistical analyses. Trends in mean values or frequencies of variables across subgroups of eGFR level were tested using linear regression analysis or logistic regression analysis, respectively. Mean stenosis rates according to eGFR levels were calculated using a linear mixed model to account for correlation between vessels within a patient. Stenosis rates between vessels correlated fairly, with a correlation coefficient range of 0.21-0.32. This analysis was carried out using the procedure "MIXED" in SAS. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using the generalized estimating equation methods to deal with modeling the correlation among repeated outcomes within a patient.[25] Correlation coefficients for the probabilities of advanced atherosclerosis and calcified lesion between vessels ranged from 0.08-0.34 and 0.25-0.37, respectively. These analyses were performed using procedure "GENMOD" in SAS. Trends in relationships between eGFR levels and risk of outcomes were tested by adding the median value of eGFR for each category to the relevant model. Two-tailed $P < 0.05$ was defined as statistically significant.

RESULTS

Baseline Characteristics

Table 1 lists baseline clinical and demographic characteristics of individuals included in the study according to eGFR levels. Individuals with lower eGFRs had higher systolic blood pressure and calcium-phosphorus product and lower hematocrit values. Frequency of hyper-

Table 1. Laboratory Variables and Risk Factors According to Kidney Function

	eGFR (mL/min/1.73 m²)				*P* for Trend
	≥60	45-59	30-44	<30	
eGFR (mL/min/1.73 m²)	72 (68-85)	55 (51-58)	40 (37-43)	21 (19-25)	
No. of patients	36	36	36	18	
Age (y)	84 ± 6	85 ± 6	85 ± 8	85 ± 7	0.8
Men (%)	39	39	39	39	0.9
Serum creatinine (mg/dL)	0.9 (0.8-1.0)	1.1 (1.0-1.3)	1.5 (1.3-1.7)	2.5 (2.0-3.2)	<0.001
Serum urea nitrogen (mg/dL)	16 (12-18)	19 (16-24)	24 (19-27)	39 (29-46)	<0.001
Serum albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.5	3.9 ± 0.5	3.7 ± 0.4	0.1
Systolic blood pressure (mm Hg)	141 ± 23	142 ± 29	143 ± 29	165 ± 29	0.01
Diastolic blood pressure (mm Hg)	73 ± 12	74 ± 14	75 ± 10	77 ± 13	0.2
Use of antihypertensive agent (%)	28	36	56	50	0.03
Hypertension (%)	61	58	78	94	0.006
Hemoglobin A_{1c} (%)	5.2 ± 0.8	5.7 ± 1.5	5.4 ± 0.8	5.4 ± 0.9	0.6
Diabetes (%)	11	22	19	22	0.3
Total cholesterol (mg/dL)	184 ± 37	190 ± 43	195 ± 53	186 ± 45	0.6
High-density lipoprotein cholesterol (mg/dL)	60 ± 17	52 ± 13	56 ± 17	53 ± 15	0.3
Triglycerides (mg/dL)	76 (65-102)	91 (81-124)	88 (68-123)	113 (70-167)	0.1
Calcium-phosphorus product (mg^2/dL^2)	29 ± 6	31 ± 5	31 ± 4	33 ± 5	0.005
Hematocrit (%)	37 ± 5	37 ± 6	35 ± 5	30 ± 6	<0.001
Smoking habit (%)	19	28	6	17	0.3
Alcoholic intake (%)	17	11	11	6	0.3
Median time from last health examination (y)	1.0 (0.5-2.0)	2.0 (0.5-2.0)	1.5 (0.5-3.0)	1.0 (0-2.0)	0.7
Causes of death					
Malignant neoplasms (%)	28	31	28	0	0.2
Heart diseases (%)	17	17	11	11	0.1
Cerebrovascular diseases (%)	17	11	3	11	0.4
Other diseases of circulatory system (%)	0	6	6	6	0.2
Infectious diseases (%)	17	19	33	22	0.5
Other causes (%)	19	6	8	33	0.08

Note: Values expressed as mean ± SD, frequency, or median (Q1-Q3). Hypertension was defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive agent. Diabetes was defined as hemoglobin A_{1c} level ≥ 6.0%. Trends were tested using linear regression analysis for continuous variables or logistic regression analysis for categorical variables. Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.0167; serum creatinine in mg/dL to μmol/dL, ×76.26; serum albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; total and high-density lipoprotein cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviation: eGFR, estimated glomerular filtration rate.

tension and use of antihypertensive agents increased significantly with decreased eGFR. Mean values or frequencies of other potential risk factors were not statistically different among eGFR levels.

Relationship Between Kidney Function and Severity of Atherosclerotic Lesions

Figure 2 shows a typical coronary artery for subgroups of eGFR levels. Age- and sex-ad-

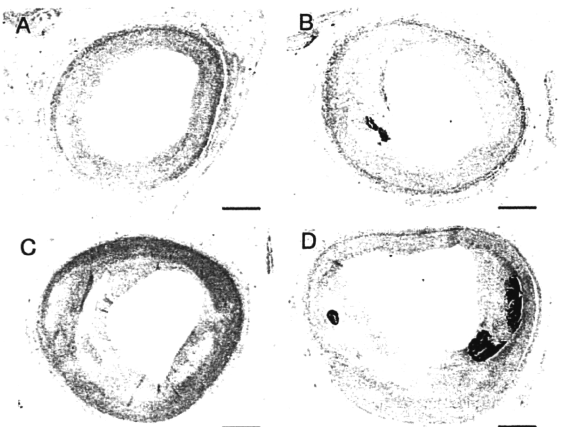

Figure 2. Typical arteries for each classification by glomerular filtration rate (GFR). (A-D) Typical light microscopic views of coronary arteries from respective cases with estimated GFRs (A) ≥60, (B) 45-59, (C) 30-44, and (D) <30 mL/min/1.73 m^2. Stenosis rates of respective arteries were (A) 36.8%, (B) 42.3%, (C) 54.2%, and (D) 58.9%. All sections were stained with hematoxylin and eosin. Scale bars = 1.0 mm.

justed mean values for coronary artery stenosis rate increased significantly with lower eGFRs (mean, 46.7% ± 1.9% [SE], 49.2% ± 1.9%, 51.9% ± 1.9%, and 53.7% ± 2.7% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; P for trend = 0.02).

Figure 3 shows proportions of atherosclerotic lesions using the AHA classification according to eGFR level. Prevalences of advanced atherosclerotic lesions defined as types IV-VI were 34.3% for eGFR ≥ 60 mL/min/1.73 m^2, 41.7% for eGFR of 45-59 mL/min/1.73 m^2, 52.3% for eGFR of 30-44 mL/min/1.73 m^2, and 52.8% for eGFR < 30mL/min/1.73 m^2. Individuals in the latter 2 categories had a significantly higher proportion of advanced atherosclerotic lesions on autopsy than those with eGFR ≥ 60 mL/min/1.73 m^2. The risk of advanced atherosclerosis was doubled in individuals with eGFR < 45 mL/min/1.73 m^2 compared with those with eGFR ≥ 60 mL/min/1.73 m^2 after adjustment for potential confounding factors, including age, sex, hypertension, diabetes, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, calcium-phosphorus product, hematocrit, smoking habit, and alcohol intake (Table 2).

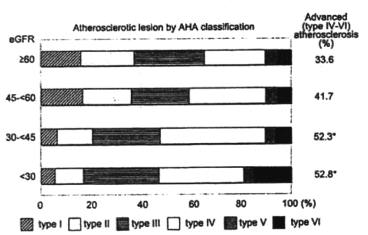

Figure 3. Proportions of atherosclerotic lesion types using American Heart Association (AHA) classification by level of kidney function. Percentages of advanced atherosclerosis (AHA types IV-VI) for each estimated glomerular filtration rate (eGFR) level is shown at the right side of the graphs. *P < 0.05 vs eGFR ≥ 60 mL/min/1.73 m^2.

Prevalence of Calcified Lesion in Coronary Artery According to Kidney Function

In a case of AHA type VI in the subgroup of eGFR < 30 mL/min/1.73 m^2, the arterial intima was thickened and associated with calcified plaque and hematoma (Fig 4).

Many coronary artery samples showed intimal calcified lesions, but there was no medial calcification in any specimen examined. Prevalences of calcified lesions were 36.5% for eGFR ≥ 60 mL/min/1.73 m^2, 37.0% for eGFR of 45-59 mL/min/1.73 m^2, 44.9% for eGFR of 30-44 mL/min/1.73

Table 2. Age- and Sex-Matched or Multivariate-Adjusted Odds Ratios for Advanced Coronary Atherosclerotic and Calcified Lesions According to Kidney Function

eGFR (mL/min/1.73 m²)	No. of Vessels Assessed	Age and Sex Adjusted[a] Matched Odds Ratio	95% Confidence Interval	P	P for Trend	Multivariate Adjusted[b] Matched Odds Ratio	95% Confidence Interval	P	P for Trend
Advanced Atherosclerosis (AHA type IV-VI)									
≥60	107	1.00	Reference		0.006	1.00	Reference		0.01
45-59	108	1.51	0.80-2.87	0.2		1.40	0.76-2.55	0.3	
30-44	107	2.22	1.11-4.43	0.02		2.02	0.99-4.15	0.05	
<30	53	2.38	1.18-4.81	0.02		3.02	1.22-7.49	0.02	
Calcified Lesion									
≥60	107	1.00	Reference		0.02	1.00	Reference		0.009
45-59	108	1.02	0.50-2.08	0.9		0.95	0.46-1.94	0.9	
30-44	107	1.43	0.71-2.89	0.3		1.43	0.69-2.95	0.3	
<30	53	2.75	1.19-6.34	0.02		4.71	1.78-12.50	0.002	

Abbreviations: AHA, American Heart Association; eGFR, estimated glomerular filtration rate.

[a]Odds ratios were adjusted for age and sex.

[b]Odds ratios were adjusted for age, sex, hypertension, diabetes, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, calcium-phosphorus product, hematocrit, smoking habit, and alcohol intake.

m^2, and 60.4% for eGFR < 30 mL/min/1.73 m^2 (P for trend = 0.02). Lower eGFR was associated with a higher prevalence of calcified coronary artery lesions. The multivariate-adjusted OR of calcified lesions was 4.71 (95% CI, 1.78-12.50) in individuals with GFR < 30 mL/min/1.73 m^2 compared with those with GFR > 60 mL/min/1.73 m^2 (Table 2).

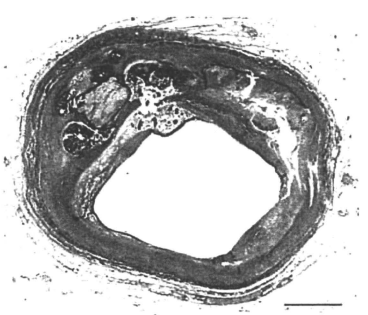

Figure 4. Typical artery of American Heart Association type VI lesion in the category glomerular filtration rate < 30 mL/min/1.73 m^2. (Masson trichrome stain; scale bar=1.0 mm.)

Association of Cardiovascular Risk Factors With Risk of Advanced Atherosclerotic Lesions and Calcified Lesions in Individuals With Decreased eGFR

Next, we assessed the relationship between the prevalence of advanced atherosclerotic lesions and cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, in individuals with eGFR < 60 mL/min/1.73 m^2 (Table 3). The risk of advanced atherosclerotic lesions tended to be higher in individuals with hypertension than in those without hypertension (OR, 1.76; 95% CI, 0.93-3.35). Individuals with diabetes had a significantly higher risk of advanced atherosclerotic lesions (OR, 2.57; 95% CI, 1.26-5.24). Likewise, hypertension and diabetes were associated significantly with increased risk of calcified lesions in individuals with eGFR < 60 mL/min/1.73 m^2 (OR, 1.88; 95% CI, 1.04-3.39 for hypertension; OR, 2.91; 95% CI, 1.56-5.45 for diabetes).

Sensitivity Analyses Using the JSN-CKDI Equation to Estimate GFR

We also estimated GFRs using the JSN-CKDI equation.[21] The distribution of JSN-eGFR (median, 49 mL/min/1.73 m^2; Q1-Q3, 35-65) was similar to that of GFR estimated using the MDRD

Table 3. Association of Cardiovascular Risk Factors With Risk of Advanced Coronary Atherosclerotic and Calcified Lesions in Individuals With Decreased Kidney Function

	No. of Vessels Assessed	Frequency of Lesion (%)	Odds Ratio	95% Confidence Interval	*P*
Advanced Atherosclerosis (American Heart Association types IV-VI)					
Hypertension					0.08
No	71	38.0	1.00	Reference	
Yes	197	51.8	1.76	0.93-3.35	
Diabetes					0.01
No	212	43.4	1.00	Reference	
Yes	56	66.1	2.57	1.26-5.24	
Dyslipidemia					0.1
No	143	42.7	1.00	Reference	
Yes	125	54.4	1.61	0.91-2.86	
Calcified Lesion					
Hypertension					0.04
No	71	33.8	1.00	Reference	
Yes	197	48.7	1.88	1.04-3.39	
Diabetes					<0.001
No	212	40.1	1.00	Reference	
Yes	56	62.5	2.91	1.56-5.45	
Dyslipidemia					0.5
No	143	42.0	1.00	Reference	
Yes	125	48.0	1.25	0.71-2.20	

Note: Hypertension defined as blood pressure ≥ 140/90 mm Hg and/or use of antihypertensive agent. Diabetes defined as hemoglobin A_{1c} level ≥ 6.0%. Dyslipidemia defined as total cholesterol level ≥ 220 mg/dL, high-density lipoprotein cholesterol level < 40 mg/dL, and/or triglyceride level ≥ 150 mg/dL. Odds ratios adjusted for age and sex.

Study equation (median, 52 mL/min/1.73 m^2; Q1-Q3, 39-64), and these values correlated well ($r = 0.98$; $P < 0.0001$). Median (Q1-Q3) JSN-eGFR values for each category of GFR estimated using the MDRD Study equation were 77 (71-83), 54 (48-56), 36 (33-39), and 18 (15-21) mL/min/1.73 m^2 for eGFR categories ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively. Sensitivity analyses using the JSN-CKDI equation to estimate GFR made a little difference in the findings. Age- and sex-adjusted mean values for coronary artery stenosis rate increased gradually with lower JSN-eGFR levels (mean, 47.3% ± 1.9% [SE], 49.4% ± 2.1%, 51.7% ± 2.0%, and 52.3% ± 2.6% for JSN-eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; *P* for trend = 0.06). Lower JSN-eGFRs were associated significantly with higher risks of advanced atherosclerosis and calcified lesions after adjusting for age and sex (*P* for trend = 0.04 for both). Individuals with JSN-eGFRs < 30 mL/min/1.73 m^2 were likely to have greater risks of advanced atherosclerosis (OR, 1.80; 95% CI, 0.70-4.64) and calcified lesions (OR, 3.90; 95% CI, 1.45-10.49) than individuals with JSN-eGFR ≥ 60 mL/min/1.73 m^2 after adjusting for the mentioned confounding factors.

DISCUSSION

This study showed a clear relationship between lower kidney function and severity of coronary atherosclerosis in autopsy samples from a general population. To the best of our knowledge, this is the first histopathologic study showing the gradual progression of coronary atherosclerosis, even in individuals with moderate CKD. Additionally, cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, were associated with higher risk of advanced coronary atherosclerosis and calcified lesion in individuals with CKD. These findings imply the

importance of the management of cardiovascular risk factors before reaching an advanced stage of CKD to reduce the risk of coronary atherosclerosis.

Several authors have reported the relationship between kidney function and coronary atherosclerosis in people with advanced kidney failure. Lindner et al[26] showed that ~35% of all deaths in patients receiving hemodialysis were caused by coronary heart disease, partly confirmed by autopsy. Cross-sectional studies also showed that more than half the predialytic patients without signs and history of angina or myocardial infarction have had significant coronary artery stenosis, proved by coronary angiography.[27,28] Additionally, uremic patients are more likely to have coronary atherosclerotic lesions with plaque, medial thickness, and calcification than nonuremic patients in an autopsy-based study.[14] In the present study, the prevalence of advanced coronary atherosclerotic lesions increased gradually, even in individuals with moderate stages of CKD. These results emphasize the importance of considering kidney function status before patients reach advanced CKD in trying to reduce the burden of coronary atherosclerosis in the general population.

Several potential mechanisms can explain the association shown. Individuals with CKD often have a higher burden of traditional cardiovascular risk factors, such as aging, increased blood pressure, diabetes, and dyslipidemia.[29] Additionally, decreased eGFR may be associated with increased levels of novel cardiovascular disease risk factors, such as inflammation, oxidative stress, anemia, and abnormal calcium-phosphate metabolism.[29-31] Several experimental findings from uremic apolipoprotein E knockout mice support these results.[32-35] In the present study, the significant association between decreased GFR and severity of coronary arteriosclerosis was observed even after adjustment for all major traditional cardiovascular risk factors and some novel factors, including anemia and abnormal calcium-phosphate metabolism. However, we were unable to assess sufficiently how these other potential confounding factors influenced study findings. Further exploration clearly is needed to map risk factors for coronary atherosclerosis in individuals with CKD.

Several limitations of our study should be discussed. First, this was a cross-sectional study; therefore, it was difficult to infer causality between CKD and risk of progression of coronary atherosclerosis. However, the findings suggested strongly that individuals with CKD should be examined for progressive coronary atherosclerosis. Second, it has been well recognized that GFR estimated using the MDRD Study equation leads to a certain degree of misclassification of eGFR levels. However, this limitation is unlikely to change our conclusions because sensitivity analysis using the JSN-CKDI equation to estimate GFR did not make material differences in the findings. Third, no information was available regarding the severity or duration of hypertension and other cardiovascular disease risk factors. Furthermore, we also have no data available for medication use, such as lipid-lowering agents and phosphate binders. This limitation may reduce the experimental accuracy to some extent. Finally, this study is based on autopsy and the proportion of aged people is extremely high. Thus, these findings might not be applicable to the general living population. Nevertheless, information gained in this study contributes meaningfully toward better understanding the pathogenesis of coronary atherosclerosis in individuals with CKD.

In conclusion, decreased eGFR is associated significantly with severity of coronary atherosclerosis. The findings emphasize that individuals with CKD should be considered a high-risk population for coronary heart disease, and cardiovascular risk factors should be monitored substantially in this population to prevent the progression of coronary atherosclerosis. Further studies are needed to elucidate the precise mechanism mediating the deterioration of atherosclerotic lesions in individuals with CKD.

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Review Article

Renal outcomes in chronic kidney disease

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ABSTRACT:

The prevalence of treated patients with end-stage renal disease (ESRD) has been increasing steadily in Japan. High ESRD prevalence could be explained by multiple factors such as better survival on dialysis therapy, luxury acceptance due to insurance system to cover dialysis therapy, and 'truly' high incidence and prevalence of chronic kidney disease (CKD). The growing elderly population may also contribute to this trend. The Japanese Society of Nephrology estimated the prevalence of CKD stage 3 as 10.4%, 7.6% within the range of 50–59 mL/min per 1.73 m² in a screened population. Strong predictors of treated ESRD shown by using community-based screening programs and an ESRD registry in Okinawa are dip-stick-positive proteinuria and hypertension. Low glomerular filtration rate per se, which is often observed in the elderly population, is not a significant predictor of developing ESRD unless associated with proteinuria. CKD is common in Japan and is expected to increase, particularly in the elderly population. Benefits of proteinuria screening and automatic reporting of estimated glomerular filtration rate on the incidence of ESRD remain to be determined.

According to the annual report of the Japanese Society for Dialysis Therapy (JSDT), the prevalence of treated end-stage renal disease (ESRD) patients has been increasing for the past 20 years (Fig. 1).[1] In the population aged 75 years and over, the prevalence is more than 0.5%. The incidence of ESRD is also increasing, particularly in those aged 75 years and over (Fig. 2). The main causes of ESRD incidence are diabetes mellitus (DM), chronic glomerulonephritis and nephrosclerosis. The incidence of DM is now more than 300 per million populations in those aged 65 years and over (Fig. 3). The mean age at start of dialysis therapy is over 65 years. There is a north (low) to south (high) gradient in the incidence and prevalence of ESRD without obvious explanation.

The CKD prevalence seemed to be increasing in Japan. According to a community-based study in Hisayama, the age-adjusted prevalence of CKD stage 3 and 4 was 4.1% in 1974, 4.8% in 1988 and 8.7% in 2002 in men, and 7.3% in 1974, 11.2% in 1988 and 10.7% in 2002 in women.[2] This secular trend may be related to both genetic and environmental factors. Low birthweight, which is associated with lower nephron number, might develop DM and hypertension and therefore increase risk of ESRD.[3] However, such data is not available in Japan. Lifestyle-related factors that are often associated with obesity and metabolic syndrome may have a role in the development and progression of CKD.[4,5]

PREDICTORS OF ESRD AMONG SCREENED SUBJECTS (Table 1)

Japan has a long history of universal screening systems including urine test for proteinuria and haematuria.[6,7] It is not mandatory, however, so the fraction of people participating has been low at approximately 20–30%. We have been investigating the predictors of ESRD using two independent registries (Okinawa Dialysis Study (OKIDS) for dialysis patients and Okinawa General Health Maintenance Association (OGHMA)) for community-based screenees.[8,9] Screenees who eventually developed ESRD were confirmed by using the two registries and medical records.

Among the commonly measured variables, significant predictors of developing ESRD were dip-stick positive proteinuria and haematuria, and hypertension.[10] We have been reporting the importance of proteinuria and hypertension. Other predictors in Table 1 are also statistically significant, but the clinical significance is less than that of

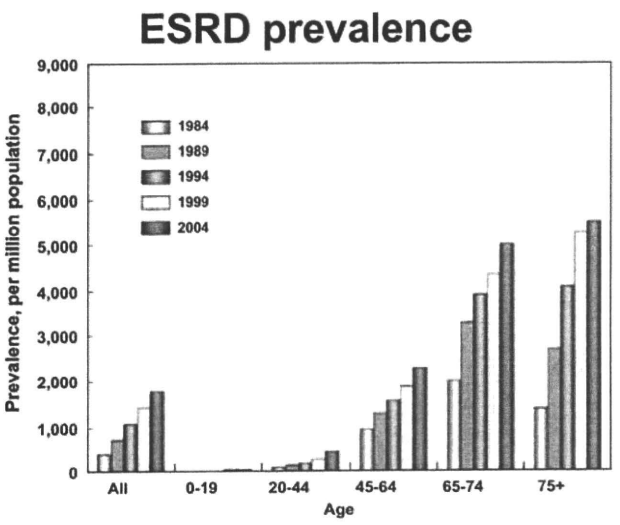

Fig. 1 Prevalence of dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

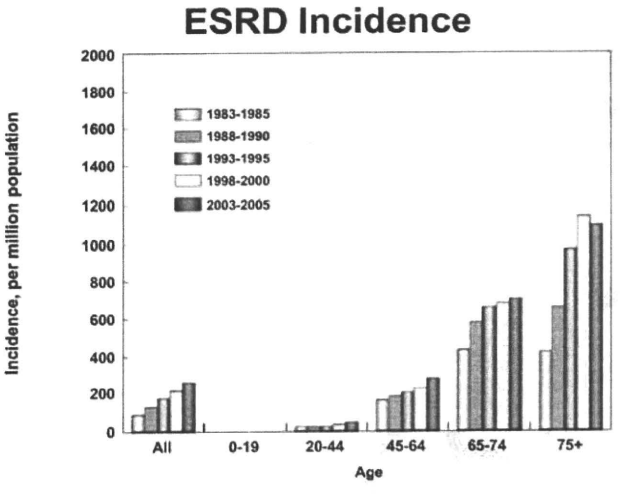

Fig. 2 Incidence of dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

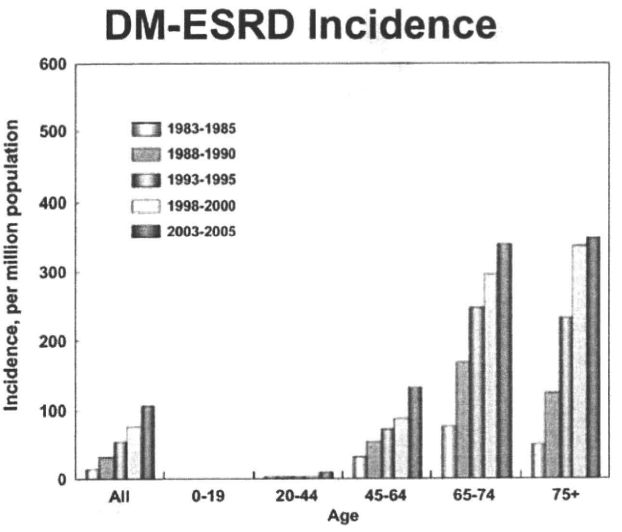

Fig. 3 Incidence of diabetes mellitus (DM) dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

Table 1 Important predictors of end-stage renal disease

1. Proteinuria
2. Hypertension
3. Hyperglycaemia
4. Hyperuricaemia
5. Anaemia
6. Obesity
7. Metabolic syndrome
8. Low glomerular filtration rate

proteinuria and hypertension.[8–13] Effects of obesity on CKD and ESRD were complex and we observed that the decrease in body mass index was a risk factor for developing CKD[14] and ESRD.[15] Low glomerular filtration rate (GFR) per se was not significant, unless otherwise associated with proteinuria.[16] The annual incidence of ESRD was approximately 1% in those with dip-stick 3+ and over and renal biopsy recipients.

The Japanese Society of Nephrology (JSN) has estimated the prevalence of CKD stage 3 to be 10.4%, 7.6% within the range of 50–59 mL/min per 1.73 m^2, in the screened population. The annual GFR decline rate was approximately 0.36 mL/min per 1.73 m^2.[17] Among those who visited twice in 10 years, GFR declined only in the aged group, 60 years and over.[18] Other than high blood pressure and proteinuria, factors related to this age-related GFR decline were not certain. Prevalence of proteinuria, hypertension, DM, anaemia, and metabolic syndrome increased with the decline in estimated GFR (eGFR).

UNIVERSAL OR TARGETED SCREENING FOR CKD?

In April 2008, the Ministry of Health, Labour and Welfare started Tokutei-Kenshin for all residents aged 40–74 years. This strategy is to implement lifestyle modification for those diagnosed with metabolic syndrome. Initially, the urine test was set as optional, not mandatory for this program. This screening program was not originally planned to detect CKD. The cost for measuring microalbuminuria is only covered for DM patients without obvious nephropathy and the test can be repeated every 3 months. The cost is ¥1150 (>$US 10). A

cost–benefit analysis examining the frequency and extent of screening including microalbuminuria is currently under survey in Japan.

ONGOING STUDIES

Both the JSN and JSDT are working together to educate people and collecting evidence for preventing ESRD and related cardiovascular disease (CVD). The JSN has published the GFR estimation equation based on inulin clearance.[19] Using the nationwide registry, Japan Kidney Disease Registry (J-KDR), several cohort studies are underway.

Late referral to nephrologists, which is defined as dialysis started within 1 year after referral is common.[20,21] According to the 2007 annual report of the JSDT, the late referral rate was 69.3%, and that of less than 1 month was 37.7%. Such 'late referral' has a negative impact on survival after starting dialysis. Preliminary result of the JSDT supports the notion that the longer the duration of pre-haemodialysis (HD) treatment, the better the survival. The explanations of such an observation remained speculative. Differences in the control of hypertension, nutritional status and comorbid conditions identified by different nephrologists might play a role.[22] The Japan Incident Dialysis Cohort Study (J-IDCS) has been started to examine the current status of the incidence of Japanese HD patients and how they progress into ESRD.

There are two other ongoing projects in Japan. The Japanese Government (Ministry of Health and Labour) assigned CKD as a national target disease for the strategic medical research in 2007. The Japan Kidney Foundation was asked to launch the investigation: project leader, Professor K Yamagata; Frontier of Renal Outcome Modifications in Japan (FROM-J). The main objective of this research is to observe the CKD progression between two treatment strategies such as intervention A and B, and the target number of total patients is 2500. In both groups, CKD patients are treated by a general physician (Kakarituke doctor) based on the CKD practice guide of the JSN. In intervention B, patients are also followed by a registered dietician and monitored by outside personnel every month. The primary outcomes are: (i) the dropout rate; (ii) the referral rate to registered nephrologists; and (iii) progression rate of CKD to ESRD. The expected difference in the incidence in ESRD is 15% in 5 years between the two groups. This target was set using the following reports. The 2002 DM survey conducted by the Ministry of Heath, Labour and Welfare of Japan stated that only 33.3% of patients had been controlled their HbA1c less than 6.5%; that hypertension is not adequately controlled because less than 50% of subjects with hypertension are taking medications for hypertension in Ibaraki, Japan;[23] and renin angiotensin inhibitors have been used less in the area where the incidence of ESRD is high.[24] Sorensen *et al.* reported that significant decrease (15%) in DM nephropathy was achieved with aggressive management of blood pressure and glucose.[25] In this study, GFR change will also be followed using the JSN original equation.[19] The second is the chronic kidney disease-Japan cohort (CKD-JAC).[26] The natural course of CKD has not been studied in a large cohort of patients. Risk factors of CKD progression with respect to the development of CVD are not known in Japan. The study will enrol 3000 CKD patients, eGFR 10–59 mL/min per 1.73 m^2, in 18 clinical centres around Japan. Each clinical centre will enrol approximately 200 patients over 12 months and monitoring the incidence of ESRD, CVD and all-cause mortality will be determined in 4 years. The study will also examine the relationship between eGFR and quality of life. The enrolment was started in September 2007.

CONCLUSION

Japan is an emerging 'elderly' society. CKD is common in Japan and is expected to increase, particularly in the elderly population. Proteinuria and hypertension are common denominators of CVD, DM, obesity and metabolic syndrome. Further studies are necessary to determine the benefits of proteinuria screening and automatic reporting of eGFR on the incidence of ESRD. More research is needed to determine the natural course of CKD progression, particularly in the elderly population.

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