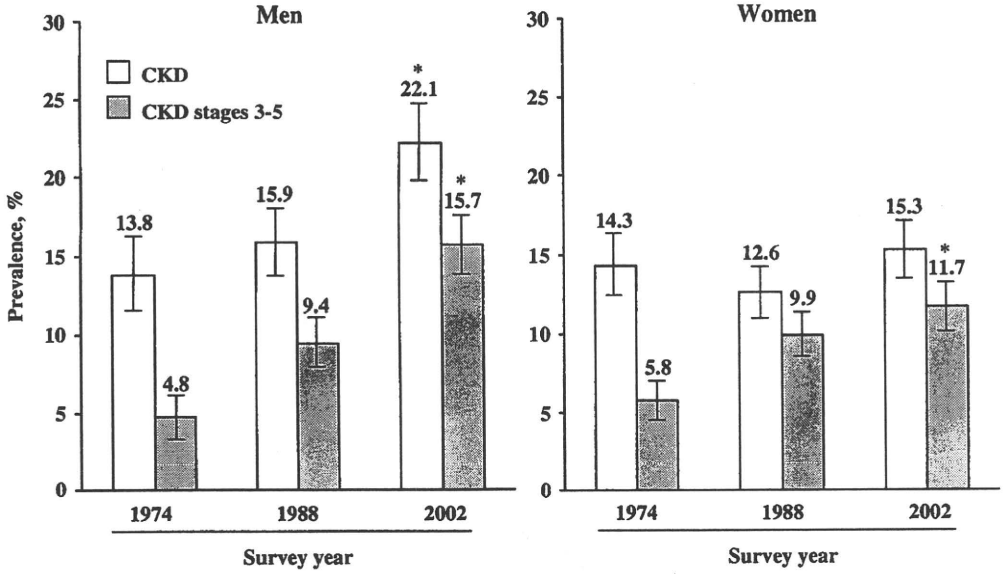
Table 1. Age-adjusted prevalence and mean values of risk factors in 1974, 1988 and 2002 by sex

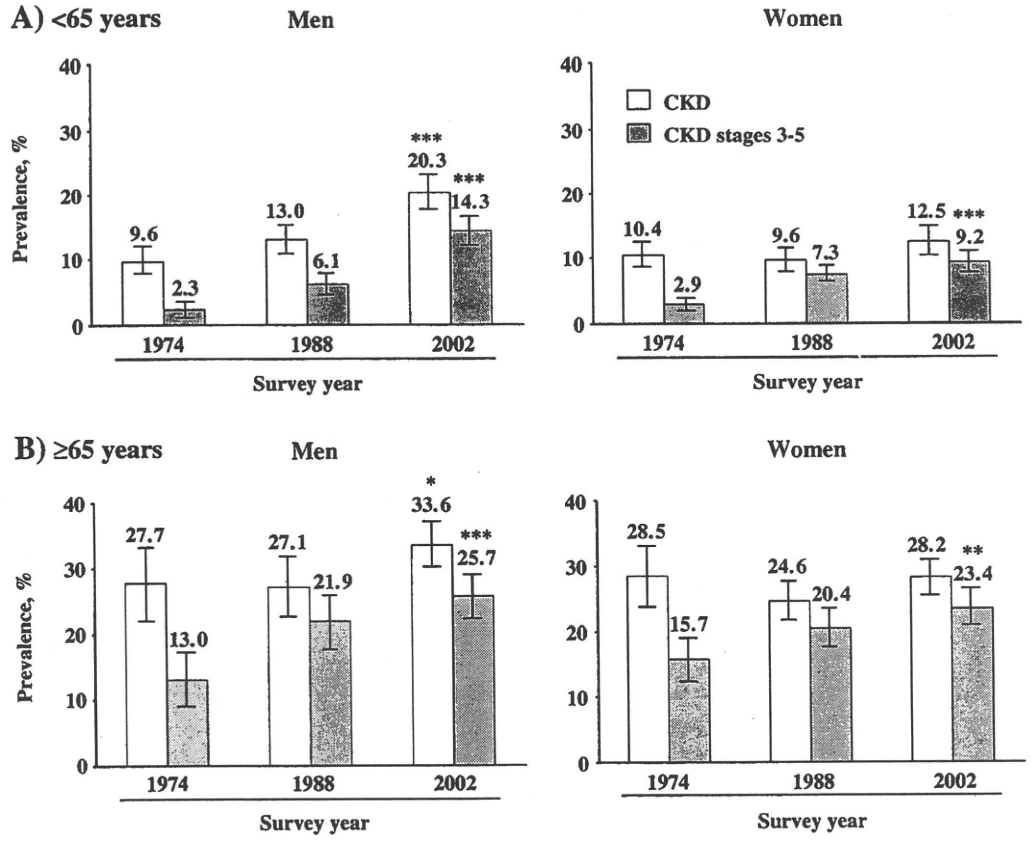
	Men				Women			
	1974 n = 911	1988 n = 1165	2002 n = 1414	P for trend	1974 n = 1207	1988 n = 1576	2002 n = 1883	P for trend
Age, years	56 ± 11	59 ± 12	61 ± 12	<0.001	57 ± 12	60 ± 12	62 ± 13	<0.001
Systolic blood pressure, mmHg	139 ± 21	136 ± 21	134 ± 21	<0.01	141 ± 21	134 ± 21	129 ± 21	<0.01
Diastolic 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.

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 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

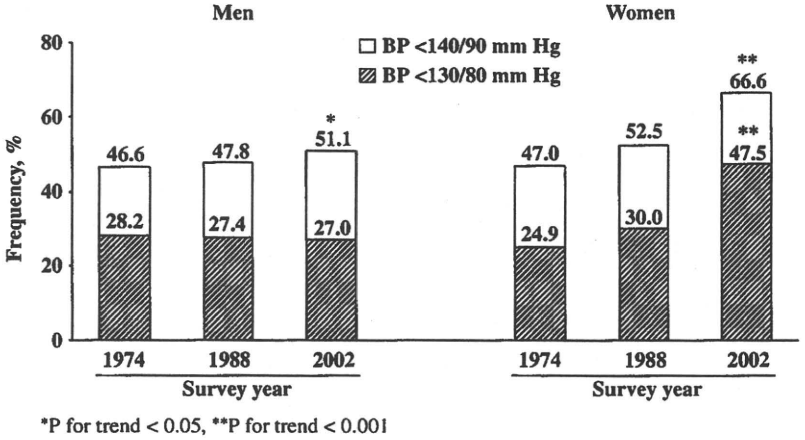


Fig. 3. Age-adjusted frequencies of well-controlled blood pressure in subjects with CKD in 1974, 1988 and 2002 by sex.

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.

(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 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

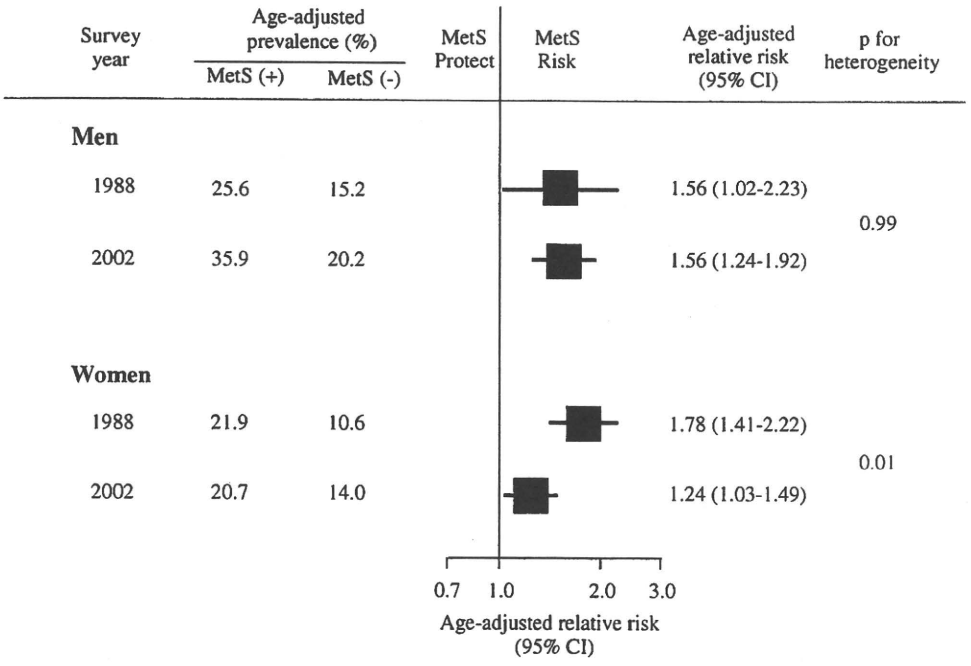


Fig. 4. Age-adjusted RR of metabolic syndrome (MetS) on the presence of CKD in 1988 and 2002 by sex.

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 proportion 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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ORIGINAL INVESTIGATIONS

Pathogenesis and Treatment of Kidney Disease

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.

Am J Kidney Dis 55:21-30.

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).

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.

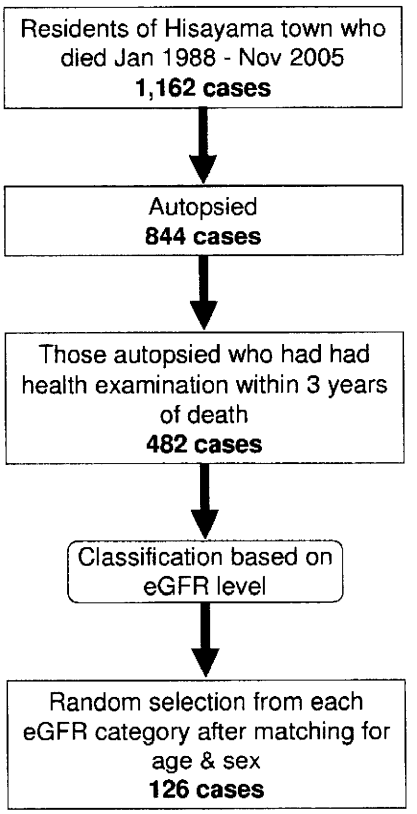

Figure 1. Flow diagram for study enrollment. Abbreviation: eGFR, estimated glomerular filtration rate.

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 (mg²/dL²)	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-

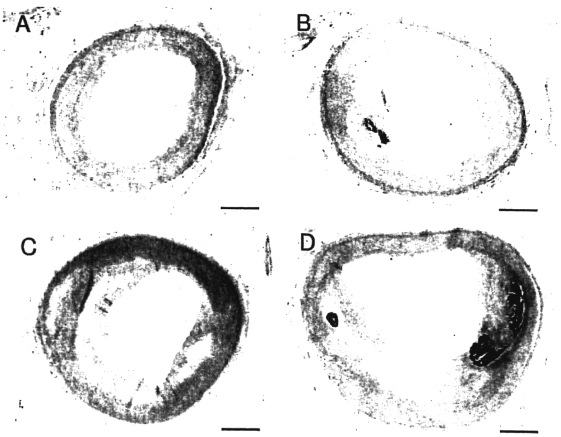

Figure 2. Typical arteries for each classification by glomerular filtration rate (GFR). (A-D) Typical light microscopic views of coronary arteries from respective cases with estimated GFRs (A) ≥60, (B) 45-59, (C) 30-44, and (D) <30 mL/min/1.73 m^2. Stenosis rates of respective arteries were (A) 36.8%, (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).

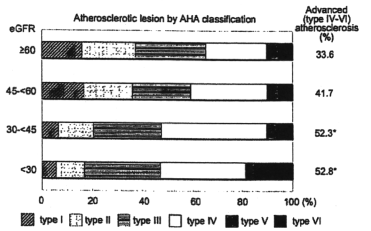

Figure 3. Proportions of atherosclerotic lesion types using American Heart Association (AHA) classification by level of kidney function. Percentages of advanced atherosclerosis (AHA types IV-VI) for each estimated glomerular filtration rate (eGFR) level is shown at the right side of the graphs. *P < 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).

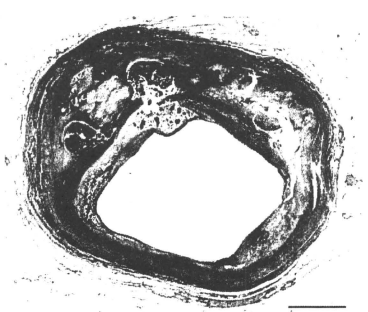

Figure 4. Typical artery of American Heart Association type VI lesion in the category glomerular filtration rate < 30 mL/min/1.73 m^2. (Masson trichrome stain; scale bar=1.0 mm.)

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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Impact of Glucose Tolerance Status on Development of Ischemic Stroke and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Few studies have shown the association between glucose tolerance status defined by a 75-g oral glucose tolerance test and the development of different types of cardiovascular disease.

Methods—A total of 2421 community-dwelling Japanese subjects aged 40 to 79 years who underwent the oral glucose tolerance test were followed up for 14 years.

Results—In multivariable analysis, the risks of ischemic stroke in both sexes and coronary heart disease (CHD) in women were significantly higher in subjects with diabetes determined by the World Health Organization criteria than in those with normal glucose tolerance even after adjustment for other confounding factors, but such association was not seen for CHD in men (ischemic stroke: adjusted hazard ratio [HR]=2.54, P=0.002 in men; adjusted HR=2.02, P=0.03 in women; CHD: adjusted HR=1.26, P=0.47 in men; adjusted HR=3.46, P=0.002 in women). Similar associations were observed for fasting plasma glucose levels of ≥7.0 mmol/L (ischemic stroke: adjusted HR=2.15, P=0.03 in men; adjusted HR=2.10, P=0.045 in women; CHD: adjusted HR=1.29, P=0.47 in men; adjusted HR=3.83, P=0.003 in women) and for 2-hour postload glucose levels of ≥11.1 mmol/L (ischemic stroke: adjusted HR=2.71, P=0.003 in men; adjusted HR=2.19, P=0.03 in women; CHD: adjusted HR=1.58, P=0.16 in men; adjusted HR=4.44, P<0.001 in women). The age-adjusted incidences of ischemic stroke and CHD did not significantly increase in subjects with impaired fasting glycemia or impaired glucose tolerance in either sex.

Conclusions—Our findings suggest that diabetes is an independent risk factor for ischemic stroke in both sexes and CHD in women in the Japanese population. (***Stroke.* 2010;41:203-209.)**

Key Words: coronary heart disease ■ diabetes ■ ischemic stroke ■ oral glucose tolerance test ■ prospective study

Cardiovascular disease continues to be a major global public health concern. Investigations into glucose tolerance levels and cardiovascular disease have become increasingly important, because the impact of diabetes on cardiovascular disease is considered to be rising due to the rapid increase in the worldwide prevalence of diabetes mellitus in recent years. A number of epidemiological studies have demonstrated that Type 2 diabetic subjects have approximately 2.0 to 4.0 times higher risk of cardiovascular disease compared with nondiabetic subjects.[1–13] However, most of these studies had important limitations. In many cohort studies used to investigate this issue, the outcomes were evaluated using mortality data.[3–9,11,12] Because nonfatal events were not included in these studies, the results may not have represented the true association between glucose tolerance levels and cardiovascular disease. Thus, prospective studies using incidence data would provide further information for predicting cardiovascular disease. In addition, the methods used to define diabetes have varied among the epidemiological studies, ranging from administration of questionnaires to measurement of casual blood glucose levels or fasting plasma glucose (FPG) alone.[1,2,11,12] Furthermore, many investigators have evaluated cardiovascular generally, rather than by type, and did not separately evaluate sex, although it is well known that the effects of each risk factor are different for each type of cardiovascular disease and sex. Thus, there have been few cohort studies investigating the associations between glucose tolerance levels, defined by a 75-g glucose tolerance test (OGTT), and the risks of developing stroke and coronary heart disease (CHD) in each sex in Asian populations.

The purpose of the present study was to address the association between glucose tolerance levels and the devel-

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opment of ischemic stroke and CHD in a prospective study of a defined community-dwelling Japanese population, all members of which underwent the OGTT.

Materials and Methods

Study Population

In 1988, a screening survey for the present study was performed in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan.[14] Of a total 3227 residents aged 40 to 79 years on the town registry, 2587 (participation rate, 80.2%) consented to participate in the examination and underwent a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 due to nausea or general fatigue during the ingestion of glucose, a total of 2480 subjects completed the OGTT. From a total of 2490 subjects including 10 on insulin therapy, 68 who had a history of stroke or CHD based on questionnaires and medical records, and one who died before follow-up was started, were excluded. The remaining 2421 (1037 men and 1384 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed up prospectively for 14 years, from December 1988 to November 2002, by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved from town. We also established a daily monitoring system among the study team, local physicians, and members of the town's health and welfare office. Using this system, we gathered information on new events of cardiovascular disease, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his or her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. Additionally, when a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 418 subjects died, of whom 312 (74.6%) underwent autopsy.

Definition of Cardiovascular Events

In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for ≥24 hours. The diagnosis and classification of stroke were determined on the basis of clinical information, including brain CT and MRI, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. Ischemic stroke was classified as either lacunar or nonlacunar infarction based on the Classification of Cerebrovascular Disease III criteria proposed by the National Institute of Neurological Disorders and Stroke.[15] In brief, lacunar infarction was diagnosed as the presence of a relevant brain stem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging and no evidence of cerebral cortical or cerebellar impairment. Patients who had typical clinical findings of lacunar infarction and a negative imaging were also categorized as cases of lacunar infarction. The other ischemic strokes were defined as cases of nonlacunar infarction.

CHD included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, and coronary artery disease treated by coronary artery bypass surgery or angioplasty. Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) evolving diagnostic electrocardiographic changes; (3) cardiac enzyme levels more than twice the upper limit of normal range; and (4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes.

During the follow-up, we identified 132 cases of ischemic stroke (for men, 61 total, or 27 lacunar and 34 nonlacunar infarctions; for women, 71 total, or 42 lacunar and 29 nonlacunar infarctions) and 112 CHD events (75 men and 37 women). All of the ischemic stroke cases underwent brain imaging.

Risk Factors

At the baseline examination, we performed the OGTT after at least a 12-hour overnight fast. Plasma glucose levels were determined by the glucose-oxidase method. FPG and 2-hour postload glucose (PG) levels were divided into 4 categories: for FPG: <5.6, 5.6 to 6.0, 6.1 to 6.9, and ≥7.0 mmol/L; for 2-hour PG: <6.7, 6.7 to 7.7, 7.8 to 11.0, and ≥11.1 mmol/L. Glucose tolerance status was also defined by the 1998 World Health Organization criteria[16]; namely, for normal glucose tolerance (NGT), FPG <6.1 and 2-hour PG <7.8; for hyperglycemia, FPG ≥6.1 and/or 2-hour PG ≥7.8; for impaired fasting glycemia (IFG), FPG 6.1 to 6.9 and 2-hour PG <7.8; for impaired glucose tolerance (IGT), FPG <7.0 and 2-hour PG 7.8 to 11.0; and for diabetes mellitus, FPG ≥7.0 mmol/L and/or 2-hour PG ≥11.1 mmol/L. Total and high-density lipoprotein cholesterol levels were determined enzymatically.

Blood pressure was measured 3 times using a sphygmomanometer after at least 5 minutes of rest; the average of 3 measurements was used for the analysis. Hypertension was defined as blood pressure levels of ≥140/90 mm Hg or current treatment with antihypertensive agents. Body mass index (kg/m^2) was used as an indicator of obesity. Electrocardiographic abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3 to 1) or ST depression (4 to 1, 4 to 2, or 4 to 3). Each participant completed a self-administered questionnaire covering medical history, antidiabetic and antihypertensive treatments, smoking habits, alcohol intake, and leisure time activity. Smoking habits and alcohol intake were classified as either current use or not. Those subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

Statistical Analysis

The SAS software package Version 9.2 (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses. Incidence was calculated by a person-year method and was adjusted for age by the direct method using 10-year age groupings. The age- and multivariable-adjusted hazard ratios (HRs) and their 95% CIs were estimated using the Cox proportional hazards model.

Ethical Considerations

This study was conducted with the approval of the Ethics Committee of Kyushu University, and written informed consent was obtained from the participants.

Results

The baseline characteristics of the subjects are summarized by sex in Table 1. Mean values of age and body mass index did not differ between the sexes. The means of FPG, 2-hour PG, and systolic and diastolic blood pressures and frequencies of diabetes, hypertension, electrocardiographic abnormalities, smoking habits, alcohol intake, and regular exercise were higher in men than in women, whereas women had higher concentrations of total and high-density lipoprotein cholesterol.

The age-adjusted incidences and age-adjusted and multivariable-adjusted HRs of ischemic stroke and CHD according to FPG levels are shown in Table 2. The age-adjusted incidences of ischemic stroke and CHD did not differ between subjects with FPG levels of <5.6 mmol/L and those with FPG levels of 5.6 to 6.0 mmol/L in either sex. In women, the age-

Table 1. Characteristics of Subjects by Sex, 1988

	Men (n=1037)	Women (n=1384)
Age, years	57 (10)	58 (10)
Fasting plasma glucose, mmol/L	5.9 (1.3)	5.7 (1.3)
2-hour PG, mmol/L	7.7 (4.0)	7.4 (3.3)
Diabetes, %	15.1	9.7
Systolic blood pressure, mm Hg	134 (20)	131 (20)
Diastolic blood pressure, mm Hg	81 (11)	76 (11)
Hypertension, %*	43.3	34.8
Electrocardiographic abnormalities, %†	19.6	12.6
Body mass index, kg/m^2	22.9 (2.9)	23.0 (3.2)
Total cholesterol, mmol/L	5.07 (1.07)	5.51 (1.05)
High density lipoprotein cholesterol, mmol/L	1.25 (0.31)	1.33 (0.29)
Current smoking, %	50.1	6.7
Current alcohol use, %	62.2	9.0
Regular exercise, %	11.2	9.0

All values are given as the mean (SD) or as a percent.
*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
†Minnesota Codes 3–1, 4–1, 4–2, or 4–3.

adjusted incidence and HR of ischemic stroke were significantly higher in subjects with FPG levels of 6.1 to 6.9 mmol/L than in those with the FPG levels of <5.6 mmol/L; however, this association was attenuated after adjustment for the following confounding factors: age, systolic blood pressure, electrocardiographic abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise. An FPG level of ≥7.0 mmol/L was a significant risk factor for ischemic stroke in both sexes and for CHD in women, even after adjustment for the previously mentioned confounding factors (ischemic stroke: multivariable-adjusted HR=2.15, 95% CI, 1.07 to 4.31, P=0.03 in men; multivariable-adjusted HR=2.10, 95% CI, 1.02 to 4.35, P=0.045 in women; CHD: multivariable-adjusted HR=3.83, 95% CI, 1.59 to 9.25, P=0.003 in women).

Table 3 presents data of the analyses for ischemic stroke and CHD according to 2-hour PG levels. Compared with subjects with 2-hour PG levels of <6.7 mmol/L, the age-adjusted incidences and multivariable-adjusted HRs of ischemic stroke in both sexes and CHD in women were significantly higher in those with glucose levels of ≥11.1 mmol/L (ischemic stroke: multivariable-adjusted HR=2.71, 95% CI, 1.41 to 5.20, P=0.003 in men; multivariable-adjusted HR=2.19, 95% CI, 1.07 to 4.48, P=0.03 in women; CHD: multivariable-adjusted HR=4.44, 95% CI, 1.85 to 10.6, P<0.001 in women). Subjects with a prediabetic range of 2-hour PG levels did not have an increased risk of either ischemic stroke or CHD.

Finally, the relationships between glucose tolerance levels defined by the World Health Organization criteria and the risks of ischemic stroke and CHD are displayed in Table 4. Compared with those in women with NGT, the age-adjusted incidences and HRs of ischemic stroke and CHD were significantly increased in women with hyperglycemia, but these associations disappeared after adjustment for other confounding factors. In regard to subtypes of hyperglycemia, the age-adjusted incidences and HRs of ischemic stroke and CHD did not significantly increase in those with IFG or IGT

Table 2. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Cardiovascular Diseases According to FPG Levels

	FPG Level, mmol/L	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	P	Multivariable-Adjusted HR (95% CI)	P
Ischemic stroke								
Men	<5.6	5391	26	5.4	1 (referent)		1 (referent)	
	5.6 to 6.0	3791	13	4.0	0.70 (0.36 to 1.36)	0.29	0.66 (0.33 to 1.29)	0.22
	6.1 to 6.9	1909	9	4.7	0.85 (0.40 to 1.82)	0.68	0.68 (0.30 to 1.54)	0.36
	≥7.0	1170	13	11.7	2.06 (1.06 to 4.00)	0.03	2.15 (1.07 to 4.31)	0.03
Women	<5.6	9707	28	3.4	1 (referent)		1 (referent)	
	5.6 to 6.0	4821	18	3.9	1.11 (0.61 to 2.00)	0.74	0.98 (0.54 to 1.79)	0.95
	6.1 to 6.9	1733	14	7.1	2.01 (1.05 to 3.84)	0.03	1.59 (0.80 to 3.13)	0.18
	≥7.0	1107	11	9.6	2.47 (1.22 to 4.97)	0.01	2.10 (1.02 to 4.35)	0.045
CHD								
Men	<5.6	5450	33	7.0	1 (referent)		1 (referent)	
	5.6 to 6.0	3808	16	4.7	0.68 (0.38 to 1.24)	0.21	0.67 (0.37 to 1.23)	0.20
	6.1 to 6.9	1942	14	7.3	1.01 (0.54 to 1.90)	0.97	0.80 (0.42 to 1.54)	0.50
	≥7.0	1195	12	9.9	1.50 (0.77 to 2.90)	0.23	1.29 (0.65 to 2.58)	0.47
Women	<5.6	9844	12	1.4	1 (referent)		1 (referent)	
	5.6 to 6.0	4893	9	1.8	1.31 (0.55 to 3.10)	0.55	1.13 (0.47 to 2.71)	0.78
	6.1 to 6.9	1815	6	2.5	1.99 (0.74 to 5.36)	0.17	1.36 (0.49 to 3.81)	0.56
	≥7.0	1138	10	7.0	5.30 (2.28 to 12.35)	<0.001	3.83 (1.59 to 9.25)	0.003

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 3. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Cardiovascular Diseases According to 2-Hour PG Levels

	Two-Hour PG Levels, mmol/L	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	*P*	Multivariable-Adjusted HR (95% CI)	*P*
Ischemic stroke								
Men	<6.7	6253	25	4.4	1 (referent)		1 (referent)	
	6.7 to 7.7	2246	7	3.5	0.81 (0.35 to 1.87)	0.61	0.84 (0.36 to 1.96)	0.68
	7.8 to 11.0	2363	13	5.5	1.22 (0.62 to 2.38)	0.57	1.05 (0.52 to 2.13)	0.89
	≥11.1	1399	16	10.9	2.66 (1.42 to 4.98)	0.002	2.71 (1.41 to 5.20)	0.003
Women	<6.7	8728	25	3.3	1 (referent)		1 (referent)	
	6.7 to 7.7	3982	17	5.3	1.51 (0.82 to 2.80)	0.19	1.29 (0.69 to 2.44)	0.43
	7.8 to 11.0	3374	15	3.8	1.18 (0.62 to 2.24)	0.62	0.99 (0.51 to 1.92)	0.96
	≥11.1	1284	14	10.3	2.80 (1.45 to 5.40)	0.002	2.19 (1.07 to 4.48)	0.03
CHD								
Men	<6.7	6239	33	6.0	1 (referent)		1 (referent)	
	6.7 to 7.7	2277	9	4.7	0.78 (0.37 to 1.63)	0.50	0.73 (0.34 to 1.55)	0.41
	7.8 to 11.0	2430	18	7.3	1.20 (0.67 to 2.13)	0.54	0.97 (0.53 to 1.77)	0.93
	≥11.1	1449	15	11.5	1.82 (0.99 to 3.34)	0.06	1.58 (0.83 to 3.00)	0.16
Women	<6.7	8858	11	1.4	1 (referent)		1 (referent)	
	6.7 to 7.7	4079	6	1.4	1.16 (0.43 to 3.15)	0.77	0.91 (0.33 to 2.52)	0.86
	7.8 to 11.0	3430	6	1.5	1.10 (0.40 to 2.97)	0.86	0.82 (0.29 to 2.29)	0.70
	≥11.1	1323	14	8.5	6.49 (2.93 to 14.36)	<0.001	4.44 (1.85 to 10.62)	<0.001

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

in either sex. Diabetes was a significant risk factor for ischemic stroke in both sexes and for CHD in women. These significant associations also remained robust even after adjustment for the previously mentioned confounding factors (ischemic stroke: multivariable-adjusted HR=2.54, 95% CI, 1.40 to 4.63, P=0.002 in men; multivariable-adjusted HR=2.02, 95% CI, 1.07 to 3.81, P=0.03 in women; CHD: multivariable-adjusted HR=3.46, 95% CI, 1.59 to 7.54, P=0.002 in women). When ischemic stroke was classified as either lacunar or nonlacunar infarction, diabetes was an independent risk factor for lacunar infarction in women (multivariable-adjusted HR=2.65, 95% CI, 1.19 to 5.93, P=0.02) and nonlacunar infarction in men (HR=3.78, 95% CI, 1.74 to 8.19, P=0.001) after adjustment for other confounding factors (Table 5).

Discussion

Using data from a 14-year follow-up study of a defined general Japanese population, we demonstrated that diabetes defined by the OGTT is an independent risk factor for the development of ischemic stroke in both sexes and CHD in women after adjustment for other confounding factors. Furthermore, we found that diabetes significantly increased the risk of lacunar infarction in women and nonlacunar infarction in men. By contrast, an FPG level of 5.6 to 6.0 mmol/L, a newly extended range from the American Diabetes Association, was not associated with ischemic stroke or CHD in either sex. In women with the FPG levels of 6.1 to 6.9 mmol/L, the age-adjusted incidence of ischemic stroke increased significantly; however, this association was attenuated after multivariable adjustment.

Very few prospective studies have provided evidence of the associations between glucose tolerance levels defined by the OGTT and the incidence of stroke and CHD. Only investigators of the Strong Heart Study of American Indians have evaluated the association of glucose tolerance status defined by the 1998 World Health Organization criteria with the risk of developing stroke. The results showed that, compared with the subjects with NGT, subjects with diabetes had a 2-fold higher risk of stroke, but subjects with IFG or IGT did not have a higher risk.[13] In a follow-up examination of a Finnish population who was free of diabetes at baseline, diabetes that developed during the follow-up was a significant risk factor for CHD, but baseline IGT was not.[17] These findings are in accordance with those of the present study. In our study, diabetes was significantly associated with the development of ischemic stroke in both sexes as well as CHD in women, but such an association was not observed for CHD in men. Although the precise reasons for this sex difference in the CHD risk conferred by diabetes are unknown, the higher prevalence of smoking in men may be responsible for this phenomenon; a smoking habit, which is a major risk factor for CHD, is considered to increase the risk of CHD in subjects with normal glucose levels, which would weaken the association of diabetes with CHD in men. Several cohort studies indicated that elevated 2-hour PG levels of 7.8 to 11.0 mmol/L, a category of IGT, was associated with an increased mortality from cardiovascular disease.[6–8,18,19] However, there have been some epidemiological studies in which IGT was not a risk factor for cardiovascular death.[3,5,9] In the present study, IGT was not associated with the development of ischemic stroke or CHD. However, our previous study of