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Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population—the Ohasama study

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Abstract

Background. Chronic Kidney Disease (CKD) has been shown to be a risk factor for mortality as well as for morbidity such as cardiovascular disease (CVD) in the general population. However, in the context of CVD events, there is a difference in the incidence of cardiac and stroke events between Western and Asian populations. Although a high prevalence of stroke is a characteristic feature in Japanese populations, it is unclear whether CKD constitutes a risk for stroke events.

Methods. To clarify this issue, we estimated creatinine clearance and obtained dipstick tests from spot-urine samples in 1977 subjects (mean 62.9-years-old, men/women: 731/1246) from a general Japanese population. First symptomatic stroke events and all-cause mortality were analysed according to stratification of kidney function and by positive tests for macroalbuminuria using a Cox proportional hazards regression model adjusted for possible confounding factors.

Results. During the observation period (mean 7.76 years), we recorded 112 events of first symptomatic stroke and 187 deaths (58 cases due to CVD). After adjustment for all variables, we found that increases in relative hazard (RH) for the first symptomatic stroke events were associated with decreasing kidney function (RH, 3.1; 95% CI, 1.24–7.84 in Ccr < 40 ml/min, 1.9; 95% CI, 1.06–3.75 in Ccr 40–70 ml/min, ref in Ccr > 70 ml/min) and with the presence of macroalbuminuria (RH, 1.4; 95% CI, 0.80–2.41).

Conclusion. Decreased kidney function increased the risk of first symptomatic stroke events in a general Japanese population. The high prevalence of stroke in this population prompts the need for greater public awareness about risks for CKD.

Keywords: chronic kidney disease; Japanese general population; stroke

Introduction

Chronic Kidney Disease (CKD) [1] is an independent risk factor for all-cause mortality including cardiovascular disease (CVD) events among the general population in Western countries [2–5]. Recent reports from Japan have also confirmed CKD as a significant risk for CVD events and all-cause mortality [6–8], suggesting that CKD represents a major public health issue that is independent of ethnicity.

However, in the context of CVD events, there is a difference in the incidence of coronary heart disease and stroke events between Western and Asian populations [9]. A high prevalence of stroke has remained a major concern in Japan [10], where mortality resulting from stroke is 3-fold higher than that in the United States, while mortality from coronary heart disease is one-third of that in the United States [11,12]. In the atherosclerosis risk in a community (ARIC) study conducted in the United States [5], cardiac diseases represented a majority of CVD events, wherein 79.4% of CVD events were due to coronary heart disease. Thus, although the link between CKD and incidence of stroke events in the Asian population is of crucial interest, there is limited data in this area of research [6].

The present community-based longitudinal observational study aimed to explore this issue in the general Japanese population. We ascertained a significant role

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for kidney dysfunction in the development of first symptomatic stroke events as well as in all-cause and CVD-related mortality.

Subjects and methods

Design

The present report is based on a longitudinal observation of subjects who had been participating in a blood pressure (BP) measurement project in Ohasama, Iwate Prefecture (Japan) since 1987. Ohasama, a rural community, had a total population of 7496 in 1992. The socio-economic and demographic characteristics of this region and details of this project have been previously described [13]. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Study population

In Japan, annual health check-ups are available for farmers, the self-employed, pensioners and dependents aged ≥35 years. Among the residents of Ohasama, 3076 were eligible for annual health check-ups in 1992. Of the 2192 residents who participated in check-ups from 1992 to 1997, data on serum creatinine levels, dipstick tests for spot-urine and confounding factors were unavailable in 215 subjects. The present study population thus comprised 1977 individuals, representing 64% of the total eligible population.

Follow-up and outcomes

Residence in Ohasama as of 31 December 2001 was confirmed by residential registration cards. These cards are both accurate and reliable because they are used for pensions and social security benefits in Japan. Causes of death up to 31 December 2001 were investigated by referencing to the national mortality registry, in which underlying causes of death are classified by death certificates according to the recommendations of the 'International Classification of Disease, 10th revision' (ICD-10).

Incidences of stroke and transient ischaemic attack (TIA) up to 31 December 2001 were investigated by reference to the Stroke Registration System of Iwate Prefecture, the national mortality registry, National Health Insurance receipts and from interviews at the time of annual check-ups. Results were then confirmed by checking medical records at Ohasama Hospital, the only hospital in the community, where >90% of patients undergo regular check-ups. Death certificates were the sole source of information for only 2% of stroke cases. Most cases were diagnosed by computed tomography or magnetic resonance imaging of the brain. Diagnostic criteria for stroke and stroke subtypes were based on the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke [14].

Primary outcomes were defined as the first symptomatic event of stroke. We additionally analysed all cause mortality and mortality from CVD defined as death from diseases of the circulatory system (ICD-10:I00– I99).

Data collection

Serum creatinine was measured using the Jaffe assay. Kidney function was estimated by calculated creatinine clearance (Ccr) using the Cockcroft–Gault equation [15]. Diagnoses were made using a dipstick test for spot-urine (Urohemabonbix 5G08C; Bayer Medical, Japan). Positive macroalbuminuria was considered present for a dipstick result of + or more, corresponding to a urinary protein level >30 mg/dl [16]. BP was measured twice by nurses or technicians at local medical centres using an automatic USM-700F sphygmomanometer (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique (microphone method) [17] with subjects in a seated position after resting for ≥2 min. Casual BP was defined as the mean of two readings. Information on smoking status, use of antihypertensive medications at baseline, as well as history of CVD, diabetes mellitus or hypercholesterolaemia were obtained from interviews, from the results of blood examinations at the time of annual health check-ups, and from medical records at Ohasama Hospital. History of CVD was defined as disease of the circulatory system (ICD-10:I00 to I99), stroke and TIA. Subjects receiving administration of lipid-lowering drugs or displaying serum cholesterol levels ≥5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolaemia. Subjects with fasting glucose levels ≥77 mmol/l (126 mg/dl) or non-fasting glucose levels ≥11.11 mmol/l (200 mg/dl), or who used insulin or oral anti-hyperglycaemic drugs were defined as having diabetes mellitus. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Data analysis

Associations between baseline kidney function, as defined by estimated Ccr, macroalbuminuria and incidence of primary outcomes, were examined using the Cox proportional hazards regression model, adjusted for age, gender, systolic BP, BMI and smoking status, for the use of antihypertensive medications at baseline and for history of CVD, diabetes mellitus or hypercholesterolaemia. Participants who died from other causes or who were lost to follow-up were designated as censored. The dependent variable in these analyses was the number of days from the date of observation to the date of death, stroke or TIA, or censoring, respectively.

The estimated relative hazard (RH) and 95% confidence interval (95% CI) of variables were derived from the coefficient and standard error as determined by the Cox proportional hazards model. Data are shown as means±SD. Values of $P < 0.05$ were accepted as indicative of statistical significance. All statistical analyses were conducted using SAS version 9.1 software (SAS Institute, Cary, NC, USA).

Results

The mean age of the 1977 subjects was 62.9 ± 9.6 years, and the ratio of men to women was 37:63. There were 154 subjects (7.8%) who presented a positive test for urinary protein. Mean systolic/diastolic BP was 130/73 mmHg. Of all the subjects, 15.6% were classified as current or ex-smokers and 22.5% were

treated with antihypertensive medication, while 5.1, 8.8 and 37.7% subjects were classified as having a history of heart disease, diabetes mellitus or hyperlipidaemia, respectively. Mean BMI was 23.4 kg/m^2. A history of stroke was present in 83 subjects, indicating that 1914 subjects had never experienced a stroke.

The observational period averaged 7.8 ± 2.0 years. A total of 37 subjects (2%) moved away and were lost to follow-up. One hundred seventeen subjects developed first symptomatic strokes among 1914 cases who had never previously experienced a stroke. Of these, there was cerebral infarction in 78 cases, cerebral bleeding in 21 cases, subarachnoid haemorrhage in eight cases, TIA in four cases and other causes in one case. Of 187 deaths, 69 were due to neoplasma, 58 were due to CVD including stroke in 26 cases, 18 were due to respiratory disease and 42 were due to other causes (Table 1).

After the preliminary analysis, patients were stratified into three groups according to estimated Ccr levels: <40 ml/min, 40–70 ml/min and >70 ml/min. This classification was arbitrary but yielded the most powerful statistical difference with Cox analysis for all-cause mortality in terms of the magnitude of log likelihood ratio [18]. Basic characteristics of the respective groups are shown in Tables 1–3.

RH(s) for first symptomatic stroke events among subjects with negative stroke history, all-cause of mortality and CVD-related mortality adjusted for confounding factors were determined and compared with the reference group having Ccr > 70 ml/min (Figure 1).

RH for first symptomatic stroke event was 1.9 (95% CI:1.06–3.75) for Ccr 40–70 ml/min and 3.1 (95% CI:1.24–7.84) for Ccr < 40 ml/min. RH for all-cause mortality was 2.3 (95% CI:1.29–4.23), for Ccr 40–70 ml/min and 5.3 (95% CI: 2.46–11.59) for Ccr <40 ml/min. RH for CVD-related mortality was 1.6 (95% CI: 0.55–4.50), for Ccr 40–70 ml/min and 2.7 (95% CI: 0.67–10.63) for Ccr <40 ml/min.

Outcomes were also stratified by the presence or absence of macroalbuminuria after adjustment for the same factors employed in the analysis of kidney function. The RH for macroalbuminuria (as compared with negative) was 2.1 (95%CI:1.44–3.13) for all-cause mortality, was 2.8 (95% CI:1.49–5.21) for CVD-related mortality and was 1.4 (95% CI:0.80–2.41) for first symptomatic stroke (Figure 2).

When the analyses for macroalbuminuria or Ccr were adjusted beforehand by Ccr or macroalbuminuria, respectively, in addition to adjustment for basal confounding factors, nearly the same results were found.

Table 2. Subject characteristics (1)

Ccr (ml/min)	<40	40–70	70<
n	176	1246	555
Age (years old)	75.6 ± 7.2	64.5 ± 7.2	55.3 ± 9.0
Gender (male%)	34.7	35	42.2
Height (cm)	146.4 ± 8.6	151.1 ± 7.7	157.0 ± 8.1
Weight (kg)	44.4 ± 7.3	52.4 ± 7.5	62.3 ± 8.7
BMI	20.7 ± 2.7	23.0 ± 3.0	25.3 ± 3.1
SBP (mmHg)	133.0 ± 19.6	130.5 ± 17.5	130.3 ± 15.5
DBP (mmHg)	71.6 ± 11.4	72.6 ± 11.2	74.3 ± 10.4
Creatinine (mg/dl)	1.1 ± 0.3	0.9 ± 0.1	0.8 ± 0.1
TC (ml/dl)	187.0 ± 34.3	196.9 ± 34.2	196.9 ± 33.6
FBS (mg/dl)	89.0 ± 14.1	101.3 ± 18.2	110.3 ± 37.3
BS (mg/dl)	131.0 ± 67.3	118.0 ± 31.9	117.4 ± 42.7

(Mean ± SD).
SBP/DBP, systolic and diastolic blood pressure; TC, total colesterol; FBS/BS, fasting and non-fasting blood glucose.

Table 3. Subject characteristics (2)

Ccr (ml/min)	<40	40–70	70<
n	176	1246	555
Current or ex-smokers (%)	12.5	15.7	16.2
Antihypertensive medications (%)	31.8	24.2	15.7
History of cardiovascular disease (%)	10.8	5.2	2.9
Presence of hyperlipidemia (%)	21.0	28.9	29.7
Presence of diabetes mellitus (%)	21.6	17.6	19.8
Positive for macroalbumiuria (%)	30.1	1.7	5.4

Cardiovascular disease, defined as the circulatory systems (ICD-10:I00–I99) and stroke. Presence of hyperlipidemia, defined as subjects on lipid-lowering drugs or with serum choklesterol levels of ≥5.68 mmol/l (220 mg/dl). Presence of diabetes mellitus, defined as subjects on medical treatment such as insulin or antihyperglycemic drugs or subjects with a fasting glucose level of 77 mmol/l (126 mg/dl) or non-fasting glucose level of 11.11 mmol/l (200 mg/dl). Positive for proteinuria, defined as positive of dip-stick test for spot-urine.

Table 1. Outcomes

CCr (ml/min)	<40	40–70	70-	Total	*P*-value
n	176	1246	555		
All causes of death	58 (100%)	114 (100%)	15 (100%)	187 (100%)	
Cardiovascular	18 (31.0%)	32 (28.1%)	4 (26.7%)	54 (28.9%)	
Non-cardiovascular	40 (69.0%)	82 (71.9%)	11 (73.3%)	133 (71.1%)	NS
First symptomatic stroke event	20 (100%)	77 (100%)	15 (100%)	112 (100%)	
Cerebral bleeding	4 (20.0%)	12 (15.6%)	5 (33.3%)	21 (18.8%)	
Cerebral infarction	15 (75.0%)	54 (70.1%)	10 (66.7%)	79 (70.5%)	
Others	1 (5.0%)	11 (14.3%)	0 (0.0%)	12 (10.7%)	NS

(Chi-square analysis).

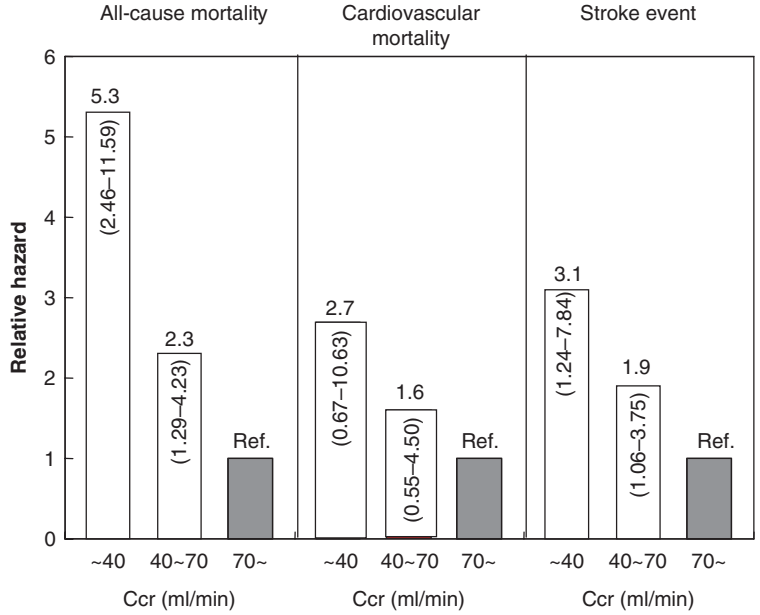

Fig. 1. Association of kidney function with the all-cause mortality, cardiovascular mortality and the first symptomatic stroke event. Relative hazard (RH) and 95% confidence intervals (CI) were adjusted for age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes. Numbers inside the bars indicate 95% CI. The lowest group was treated as the reference category.

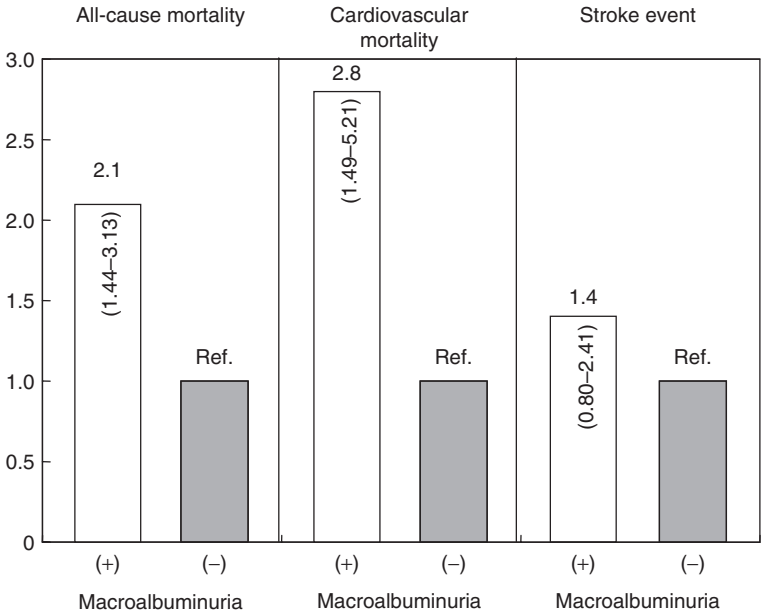

Fig. 2. Associations between macroalbuminuria and all-cause mortality, cardiovascular mortality and the first symptomatic stroke events. Relative hazard (RH) and 95% confidence intervals (CI) were adjusted for age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes.

Analysis based on the combination of both Ccr and macroalbuminuria, adjusted for the primary confounding factors, demonstrated that combination of these two factors further increased the risks (Figure 3A–C).

Discussion

The present Ohasama study was based on longitudinal observations on a general population in a rural Japanese community. This survey was unique in that diagnosis of stroke was confirmed at the Ohasama Hospital, which is the only hospital in the community, and where >90% of residents undergo regular check-ups. Furthermore, 98% of the diagnoses for all stroke events were made during radiological examinations, and only 2% of cases diagnosed by death certificates. Therefore, most of the stroke events in this community were very accurately identified.

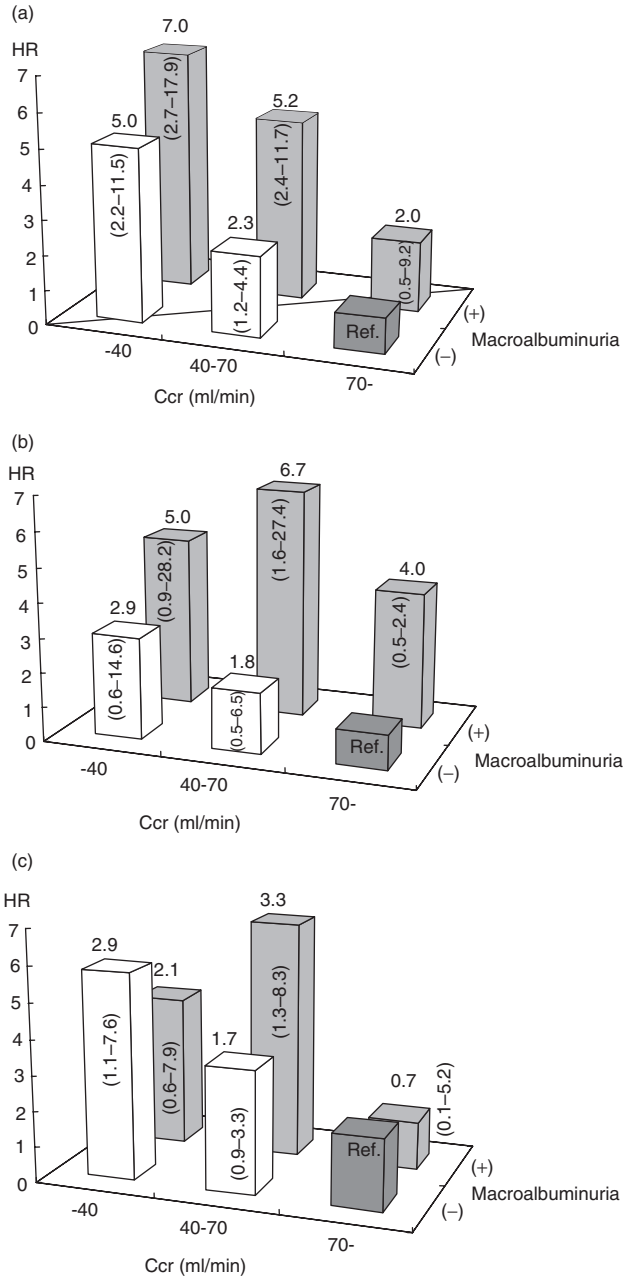

Fig. 3. Relative hazard (RH) all-cause mortality, cardiovascular mortality and the first symptomatic stroke event, according to kidney function and macroalbuminuria. RH and 95% confidence intervals (CI) were adjusted for presence of macroalbuminuria, age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes.

During the mean follow-up period of 7.76 years, a total 112 events of first symptomatic stroke and 187 deaths (31% due to CVD) were recorded. These data revealed that decreased kidney function and the presence of macroalbuminuria were independent risk factors for all-cause and CVD-related mortality, confirming a previous large-scale report from Japan [6,7]. Thus, the cohort of the present study may well represent the general Japanese population. In the analysis of first symptomatic stroke events, decreasing kidney function was associated with increasing RH (RH, 3.1 in Ccr < 40 ml/min, 1.9 in Ccr 40–70 ml/min), and the presence of macroalbuminuria tended to increase RH, but this did not reach statistical significance (RH, 1.4).

Decreased kidney function is, at least in part, related to traditional risk factors for CVD, such as age, history of CVD, smoking, atherosclerosis, diabetes and hypertension. It is known that hypertension plays a crucial role in the development of stroke events [19]. Even after adjustment for these factors, our study still revealed decreased kidney function as a significant risk factor for first symptomatic stroke events. Since cerebral infarction remained a leading disorder among stroke events in the subjects, these data indicate that decreased kidney function may constitute a risk for ischaemic stroke events. Interestingly, similar findings were reported in the UK [20], wherein high normal serum creatinine levels were a risk factor for stroke events among the general population. Furthermore, a recent study reported that mild degrees of renal dysfunction are associated with increased risk of incidental ischaemic stroke or TIA among patients with CVD [21]. Taken together, these findings indicate that a common pathological factor may be involved in the development of stroke and cardiac events in the course of CKD, and we speculate that non-classical risk factors may be involved in these mechanisms. These issues will require further clarification.

In this survey, the dipstick test was employed to test for the presence of macroalbuminuria, and proteinuria greater than + was defined as positive, which corresponds to a urinary protein level >30 mg/dl [16]. The significant links between macroalbuminuria and mortality in our subjects support findings from previous studies examining the effect of macroalbuminuria [22]. However, we unexpectedly found that macroalbuminuria was not a significant risk factor for first symptomatic stroke events in the current study. Interestingly, a recent report from Japan [6] revealed that macroalbuminuria was not a significant risk factor for death due to stroke, although it was a significant risk factor for all-cause and CVD mortality. We speculate that patients with macroalbuminuria are also likely to have systemic vasculopathy, and therefore the death events due to all-causes may be more apparent than those caused by first symptomatic stroke events. The potential importance of macroalbuminuria for stroke events warrants further study.

For the method of estimating kidney function, we could not employ the recently recommended IDMS-derived new MDRD formula to predict estimated GFR in the present study [23]. Instead, we used the Cockcroft–Gault equation even though it is not the best method. This was done because serum creatinines were measured by Jaffe assay, and the available racial coefficient in calculating the MDRD equation for the Japanese population is lacking. Thus, further studies to examine exact risk estimation based on the CKD staging are still needed.

In conclusion, decreased kidney function increased the risk for first symptomatic stroke events in a general Japanese population. The high prevalence of stroke in this population prompts the need for greater public awareness about risks for CKD.

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Conflict of interest statement. None declared.

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