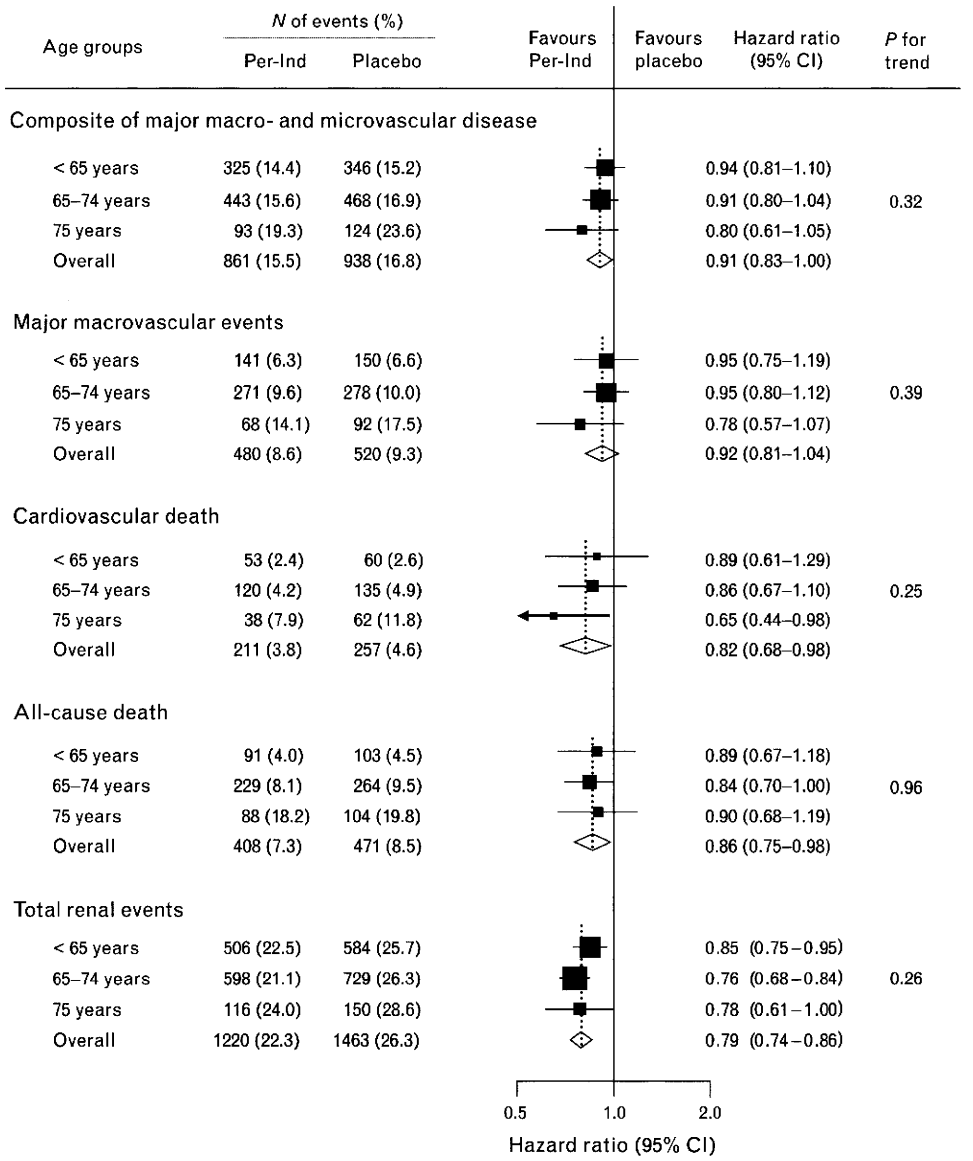
Fig. 2



The effects of perindopril–indapamide compared with placebo on the risk of major clinical outcomes according to age groups. CI, confidence interval.

heterogeneity = 0.98 for DBP). The mean SBP or DBP levels achieved over time in the active treatment groups were 133/77 mmHg (SE 0.2/0.1), 135/74 mmHg (SE 0.2/0.1) and 137/72 mmHg (SE 0.5/0.3) for patients aged below 65, 65–74 and at least 75 years, respectively.

Active treatment produced similar proportional risk reductions for the composite primary outcome of major macrovascular and microvascular disease, and for major macrovascular disease, cardiovascular death, all-cause death and total renal events across age groups (all P for heterogeneity >0.25) (Fig. 2). The absolute benefits associated with active treatment were progressively greater in older patients, reflecting their higher baseline risk (Table 2). Similar patterns of increasing absolute benefits with increasing age were observed for major macrovascular disease, cardiovascular death and all-cause death.

Tolerability of blood pressure-lowering treatment in older compared with younger patients with type 2 diabetes

The proportion of patients discontinuing study treatment for different reasons was also examined (Table 3). As

Table 2 Comparisons of the absolute risk reductions on major clinical outcome for 5 years according to age

Age groups (years)	Incidence rate over 5 years (%)[a] Per-Ind	Placebo	Absolute risk reduction for 5 years for every 1000 patients (95% CI)[b]
Composite of major macrovascular and microvascular disease			
Age <65	16.2	17.0	8 (−13 to 30)
Age 65–74	17.5	18.9	14 (−6 to 34)
Age ≥75	21.5	26.3	48 (−5 to 100)
Major macrovascular disease			
Age <65	7.1	7.4	4 (−11 to 19)
Age 65–74	10.8	11.3	5 (−11 to 22)
Age ≥75	15.8	19.6	38 (−9 to 85)
Cardiovascular death			
Age <65	2.7	3.0	3 (−6 to 13)
Age 65–74	4.8	5.5	7 (−4 to 19)
Age ≥75	8.9	13.3	44 (5–83)
All-cause death			
Age <65	4.6	5.1	5 (−7 to 18)
Age 65–74	9.1	10.7	16 (1–32)
Age ≥75	20.4	22.1	18 (−33 to 68)
Total renal events			
Age <65	25.0	28.5	35 (9–60)
Age 65–74	23.5	29.2	57 (34–80)
Age ≥75	26.7	31.7	50 (−7 to 106)

CI, confidence interval. [a] The incidences rates over 5 years were estimated under the assumption of constant probability of the event per year. [b] Absolute risk reductions in the incidence of study outcomes were calculated by subtracting the incidence in the active group from the incidence in the placebo group.

expected, the proportion of patients permanently discontinuing study treatment increased with age group, but was similar in the active treatment and placebo groups (P for trend = 0.70) (Table 3). The proportion of patients discontinuing study treatment due to participant decision or inability to attend clinic visit was lower in active treatment groups than in placebo groups. Compared with those assigned to the placebo group, those assigned to active treatment were more likely to discontinue study treatment due to cough, hypotension or dizziness. Among

Table 3 Tolerability of the randomized treatment according to age groups

Age groups	*N* of discontinuation of treatment (%) Per-Ind	Placebo	Odds ratio (95% CI)	*P* for trend	Absolute differences in the incidence of treatment discontinuation over 5 years for every 1000 patients (95% CI)[a]
Main reason for the discontinuation					
Participant decision or inability to attend clinic visit					
Age <65 years	146 (6.5)	175 (7.7)	0.83 (0.66–1.05)	0.46	13 (−2 to 29)
Age 65–74 years	296 (10.4)	346 (12.5)	0.82 (0.69–0.96)		23 (5–40)
Age ≥75 years	79 (16.4)	114 (21.7)	0.70 (0.51–0.97)		59 (9–109)
Cough					
Age <65 years	56 (2.5)	23 (1.0)	2.50 (1.53–4.08)	0.75	−17 (−25 to −9)
Age 65–74 years	107 (3.8)	41 (1.5)	2.61 (1.81–3.76)		−26 (−35 to −17)
Age ≥75 years	21 (4.3)	8 (1.5)	2.94 (1.29–6.70)		−32 (−54 to −10)
Hypotension or dizziness					
Age <65 years	22 (1.0)	7 (0.3)	3.20 (1.36–7.50)	0.63	−8 (−13 to −3)
Age 65–74 years	36 (1.3)	13 (0.5)	2.73 (1.44–5.15)		−9 (−14 to −4)
Age ≥75 years	11 (2.3)	2 (0.4)	6.09 (1.34–27.64)		−21 (−37 to −6)
Discontinuation due to serious adverse events[b]					
Age <65 years	22 (1.0)	19 (0.8)	1.17 (0.63–2.17)	0.57	−2 (−7 to 4)
Age 65–74 years	35 (1.2)	35 (1.3)	0.98 (0.61–1.57)		0 (−6 to 7)
Age ≥75 years	10 (2.1)	12 (2.3)	0.90 (0.39–2.11)		2 (−17 to 22)
Other specified reason					
Age <65 years	50 (2.2)	62 (2.7)	0.81 (0.56–1.18)	0.40	6 (−4 to 15)
Age 65–74 years	99 (3.5)	111 (4.0)	0.87 (0.66–1.14)		6 (−5 to 16)
Age ≥75 years	23 (4.8)	22 (4.2)	1.14 (0.63–2.08)		−6 (−34 to 21)
Total					
Age <65 years	296 (13.1)	286 (12.6)	1.05 (0.89–1.25)	0.70	−6 (−27 to 14)
Age 65–74 years	573 (20.2)	546 (19.7)	1.03 (0.91–1.18)		−6 (−27 to 16)
Age ≥75 years	144 (29.8)	158 (30.1)	0.99 (0.75–1.29)		3 (−55 to 61)

CI, confidence interval. [a] Absolute differences in the incidence of study treatment discontinuation were calculated by subtracting the incidence in the active group from the incidence in the placebo group, in which negative values mean a greater risk of the discontinuation of the study treatment in the active treatment group. [b] The discontinuation of study treatment due to any serious adverse events (e.g. suspected adverse drug reactions, macro or microvascular events or heart failure) occurred during follow-up periods.

patients discontinuing study treatment due to hypotension or dizziness, only very few cases of fracture of the lower leg (including femur and ankle) were reported: no patient in below 65 years, three patients (two active, one placebo) in 65–74 years and one patient (one active) in at least 75 years. Other serious adverse events were reported in similar proportions in both treatment groups. Across age groups, there was no clear difference between treatment groups in the proportions discontinuing therapy due to hyperkalaemia: two patients (one active and one placebo) in below 65 years, 10 patients (four active and six placebo) in 65–74 years and two patients (one active and one placebo) in at least 75 years. There was no evidence of any heterogeneity in the relationship between these proportions and study treatment by age group (all P for heterogeneity >0.40). In addition, the absolute risk reductions on major clinical events were greater than the absolute risk increments of suspected drug-related side effects in patients of at least 75 years. When the absolute risk reduction in the subgroup of patients of at least 75 years were offset by the number experiencing hypotension, dizziness or serious adverse event, active treatment prevented 29 primary endpoints, 19 major macrovascular events, 25 cardiovascular deaths and 31 total renal events, without severe side effects, in every 1000 patients over 5 years.

Discussion

There was no evidence of heterogeneity in the treatment effect of routine BP lowering using a fixed combination of perindopril–indapamide on the relative risks (RRs) of major macrovascular and renal outcomes, and mortality among patients aged below 65, 65–74 and above 75 years with type 2 diabetes, although, as a result of dividing the patients into these three smaller subgroups, the hazard ratios for the composite endpoint of major macrovascular and major microvascular disease were no longer statistically significant. However, compared with younger patients, older patients had greater absolute benefits of BP-lowering therapy on major macrovascular events and death, reflecting their higher risk of these events. Although the incidence of side effects increased with age, it did so to the same extent in the active treatment and placebo groups, so that the additional absolute reductions in cardiovascular risk and death were not achieved at the expense of additional side effects. Notably, the clinical severities of the major outcomes prevented by treatment were greater than the harms. These findings highlight the efficacy and safety of BP lowering with perindopril–indapamide in older people with type 2 diabetes.

Several large randomized trials [14–25] have shown benefits of BP-lowering therapy on the prevention of cardiovascular disease in older people. A meta-analysis [25] of randomized trials involving participants aged over 60 years of age with systolic hypertension showed that BP lowering reduced the risk of major cardiovascular events by 26%. The benefits of treatment with indapamide and perindopril have been also demonstrated in hypertensive individuals over 80 years of age [23,26]. This provides additional reassurance that the results observed within the ADVANCE trial are likely to be robust and broadly generalizable. Although previous observational studies [10,11] have suggested that the strength of the proportional association between BP and cardiovascular risk declines with increasing age, a recent analysis [12] based partly on observational data has shown that the effect of BP-lowering therapy on the proportional risk of coronary heart disease or stroke was reduced by 3–5% on average for each 10-year increase in age. On the contrary, a large meta-analysis [27] of randomized trials was not able to demonstrate any material influence of age on the proportional reductions in cardiovascular events produced by BP-lowering therapy, although power to detect small-to-moderate effects was limited.

The absolute risk reductions for the primary outcome and death were higher in those aged at least 75 years compared with those below 65 years. Active treatment was well tolerated in patients aged at least 75 years in the current study. Other randomized clinical trials [14,17,22,23] have confirmed the tolerability of BP-lowering therapy in older patients. Importantly, in the ADVANCE trial, the absolute benefits of the active treatment on major clinical outcomes appeared to outweigh the risk of side effects in older people.

The strengths of this study include the large sample size that allowed for precise estimations of risk according to age in patients with type 2 diabetes. The limitations of this study should also be noted. First, caution must be exercised when extrapolating results from a clinical trial population to the general population, although the broad spectrum of individuals with type 2 diabetes included in ADVANCE trial suggests that the study population should be representative of those seen in the community [35,36]. Second, there were too few patients over the age of 80 years for meaningful analysis to be done. However, the results of the HYpertension in the Very Elderly Trial (HYVET) [23] have recently confirmed the safety and efficacy of BP lowering in patients of at least 80 years, using a regimen based on the same two drugs, indapamide and perindopril, although there were few participants with diabetes in that study.

In conclusion, our findings did not demonstrate any significant differences in the treatment effects of routine BP lowering using a fixed combination of perindopril–indapamide on the RR of cardiovascular events, renal events and mortality among participants in ADVANCE trial aged below 65, 65–74 and above 75 years. The absolute benefits in the older age group were greater than in the younger age group. Furthermore, the study treatment was well tolerated, with adherence to therapy

close to that with placebo. These findings suggest that routine treatment with perindopril and indapamide can be recommended for older patients with type 2 diabetes.

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

Masaharu Nagata[1,2], Toshiharu Ninomiya[1,2], Yasufumi Doi[1,2], Koji Yonemoto[1], Michiaki Kubo[1,2], Jun Hata[1,2], Kazuhiko Tsuruya[2], Mitsuo Iida[2] and Yutaka Kiyohara[1]

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Correspondence and offprint requests to: Toshiharu Ninomiya; E-mail: nino@envmed.med.kyushu-u.ac.jp

Abstract

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

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

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

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

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

Introduction

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

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

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

Subjects and methods

Study population

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

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

Definition of CKD

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

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

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

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

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

Risk factors

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

Statistical analysis

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

Results

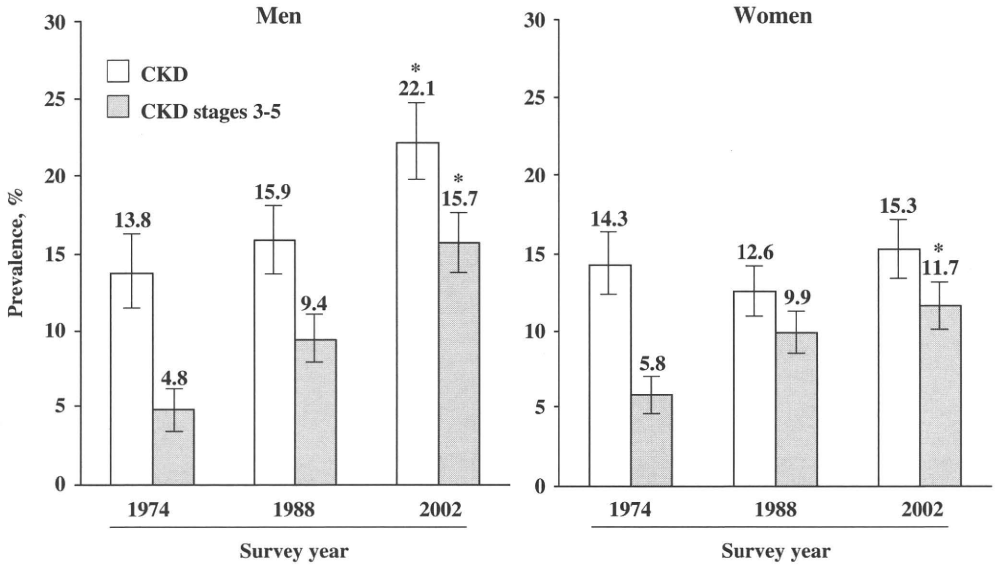
We compared the age-adjusted prevalence and mean values of risk factors among the three surveys by sex, as shown in Table 1. The prevalence of hypertension was constant in men, but decreased in women from 1974 to 2002. The prevalence of treated hypertension increased over time, whereas the prevalence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

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

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

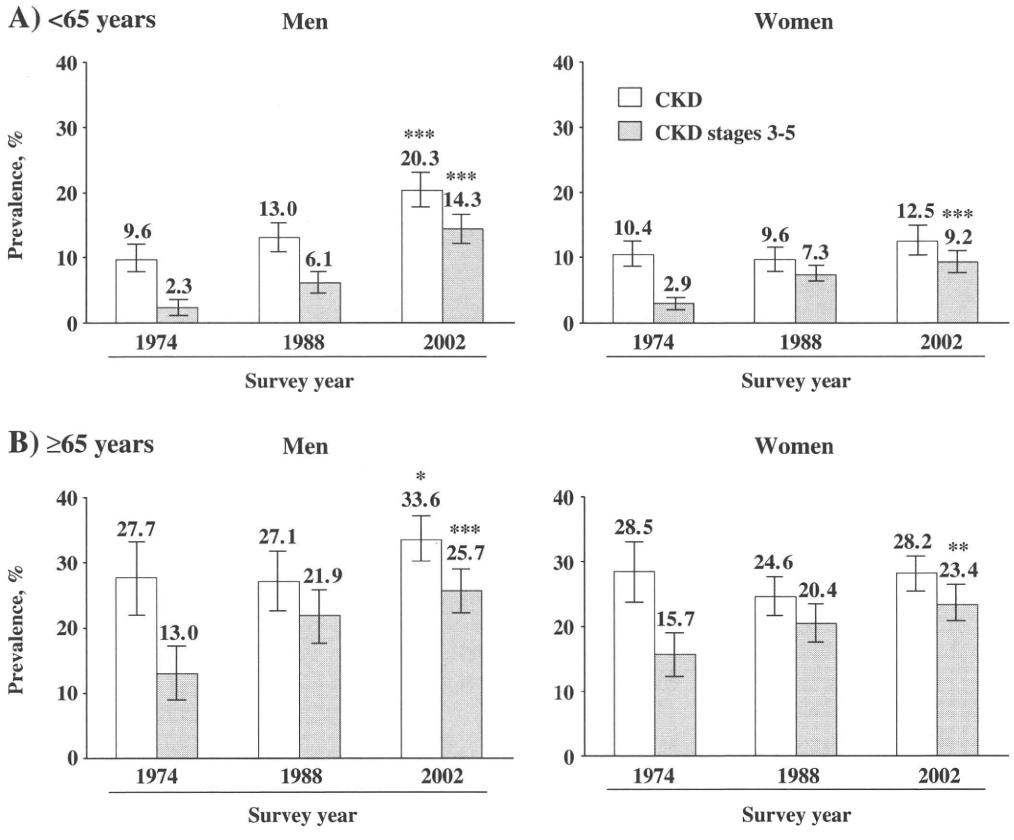
	Men				Women			
	1974 n = 911	1988 n = 1165	2002 n = 1414	P for trend	1974 n = 1207	1988 n = 1576	2002 n = 1883	P for trend
Age, years	56 ± 11	59 ± 12	61 ± 12	<0.001	57 ± 12	60 ± 12	62 ± 13	<0.001
Systolic blood pressure, mmHg	139 ± 21	136 ± 21	134 ± 21	<0.01	141 ± 21	134 ± 21	129 ± 21	<0.01
Diastolic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

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



*P for trend < 0.01

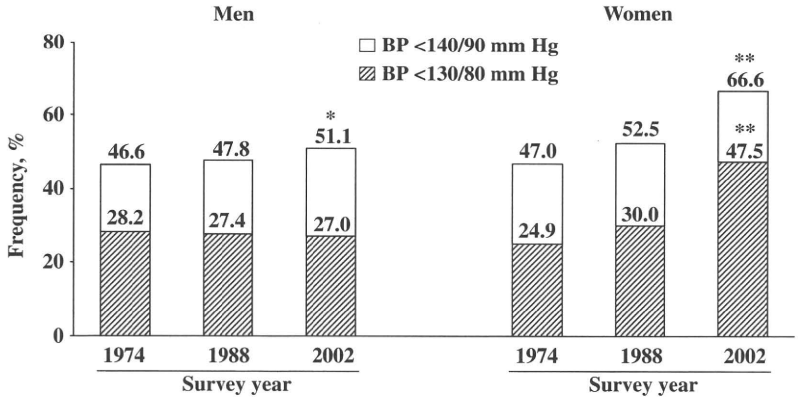
Fig. 1. Trends in the age-adjusted prevalence of CKD in 1974, 1988 and 2002 by sex.



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

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

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



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

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

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

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

[a]Adjusted for age.

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

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

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

Discussion

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

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

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

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

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

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

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

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

Conclusion

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

Supplementary data

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

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Conflicts of interest statement. None declared.

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

Charumathi Sabanayagam[1,2], Su Chi Lim[3], Tien Yin Wong[1,2,4], Jeannette Lee[5], Anoop Shankar[6] and E Shyong Tai[7]

[1]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Kent Ridge, Singapore, [2]Singapore National Eye Centre and Singapore Eye Research Institute, Singapore, Singapore, [3]Department of Medicine, Alexandra Hospital, Singapore, Singapore, [4]Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia, [5]Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [6]Department of Community Medicine, West Virginia University School of Medicine, Morgantown, WV, USA and [7]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Correspondence and offprint requests to: Sabanayagam Charumathi; E-mail: charumathi.s@nus.edu.sg

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

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Relationship between chronic kidney disease and silent cerebral infarction in patients with Type 2 diabetes

R. Bouchi, T. Babazono, N. Yoshida, I. Nyumura, K. Toya, T. Hayashi, K. Hanai, N. Tanaka, A. Ishii and Y. Iwamoto

Division of Nephrology and Hypertension, Department of Medicine, Diabetes Centre, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

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Abstract

Aims Silent cerebral infarction (SCI) is an independent risk factor for future symptomatic stroke. Although the prevalence of SCI is closely related to kidney function in non-diabetic individuals, evidence is lacking whether albuminuria and/or reduced estimated glomerular filtration rate (eGFR) independently increase the risk of SCI in diabetic patients. We therefore examined the relationships between albuminuria, eGFR and SCI in patients with Type 2 diabetes mellitus (T2DM).

Methods We studied 786 T2DM patients with an eGFR ≥ 15 ml/min 1.73/m^2, including 337 women and 449 men [mean (± SD), age 65 ± 11 years]. All patients underwent cranial magnetic resonance imaging (MRI) to detect SCI. GFR was estimated using the modified three-variable equation for Japanese subjects. Albuminuria was defined as a first morning urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g.

Results SCI was detected in 415 (52.8%) of the subjects. The prevalence of SCI was significantly associated with both elevated ACR and decreased eGFR in univariate analysis. In multivariate logistic regression analysis, urinary ACR remained independently associated with SCI after adjusting for conventional cardiovascular risk factors [odds ratio (OR) of urinary ACR per logarithmical value: 1.89, 95% confidence interval (CI) = 1.41–2.51, $P < 0.001$]; however, eGFR was no longer significantly associated with SCI (OR per ml/min 1.73/m^2 = 0.99, 95% CI = 0.98–1.00, $P = 0.095$).

Conclusion In conclusion, albuminuria but not decreased eGFR may be an independent predictor of prevalent SCI in patients with T2DM.

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Keywords albuminuria, diabetes, estimated glomerular filtration rate, silent cerebral infarction

Abbreviations ACR, albumin-to-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; SCI, silent cerebral infarction

Introduction

Chronic kidney disease (CKD), defined by the presence of albuminuria/proteinuria and/or reduced glomerular filtration rate (GFR) [1], is an independent risk factor for cardiovascular disease in both the general population [2,3] and diabetic patients [4,5]. Although the association between albuminuria and risk of cardiovascular disease has received significant attention, the contribution of reduced GFR to increased risk of cardiovascular disease remains controversial. A *post hoc* analysis from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study [6] showed that subjects with decreased estimated GFR (eGFR) but normoalbuminuria were not at increased risk of cardiovascular diseases. Similarly, we have recently shown in a prospective cohort study that lower eGFR was less likely to be associated with an increased risk of incident symptomatic stroke than albuminuria in diabetic patients [5].

Silent cerebral infarction (SCI), which has a predilection for the subcortical white matter and basal ganglia, is commonly observed on cranial magnetic resonance imaging (MRI) scans performed in the elderly and in hypertensive patients [7,8]. The presence of SCI predicts incident clinically evident stroke [9], cardiovascular disease [10] and dementia [11]. Studies have

Correspondence to: Tetsuya Babazono, MD, PhD, Division of Nephrology and Hypertension, Diabetes Center, Tokyo Women's Medical University School of Medicine, 8-1 Kawadacho, Shinjukuku, Tokyo 162-8666, Japan.
E-mail: babazono@dmc.twmu.ac.jp

suggested that reduced eGFR is associated with SCI in community-dwelling elderly persons [12] and in patients with CKD [13]; however, whether diabetes *per se* increases the risk of prevalent [7,9] or incident SCI [14,15] remains unclear. In addition, evidence is lacking whether reduced eGFR, independently of albuminuria, increases the risk of SCI in diabetic patients. We, therefore, conducted this study to assess the independent effects of albuminuria and reduced eGFR on the prevalence of SCI in patients with Type 2 diabetes mellitus (T2DM).

Patients and methods

Study population

This was a hospital-based, cross-sectional study including consecutively presenting T2DM patients who underwent cranial MRI at the Diabetes Centre, Tokyo Women's Medical University Hospital at Tokyo, Japan during the period of 1 July 2003 to 30 April 2008. MRI was generally performed for the purpose of screening for SCI, although other reasons for MRI were accepted for inclusion in the study. Patients were eligible if they were aged ≥ 20 years and their eGFR was ≥ 15 ml/min 1.73/m^2, regardless of the degree of urinary albumin excretion. Patients with Type 1 diabetes, patients undergoing renal replacement therapy, pregnant women and patients with infectious or malignant diseases were excluded. Those who had clinical and laboratory missing data were also excluded. T2DM was diagnosed according to the criteria of the World Health Organization [16].

Participants underwent a routine medical history, physical examination and blood sampling. Information regarding smoking and family history of cardiovascular disease was obtained using a standard questionnaire. Smoking history was classified as either current smoker or non-smoker. Physical examination included blood pressure measurement and anthropometry; laboratory examinations included glycated haemoglobin (HbA_{1c}), serum lipids, creatinine and urinary albumin excretion.

History of cerebrovascular disease (CVD) was defined as prior history of transient ischaemic attack and/or stroke. Clinical evidence of coronary artery disease (CAD) was defined as the presence of any of the following conditions: angina pectoris diagnosed by coronary angiography or myocardial scintigraphy, prior myocardial infarction or previous revascularization. History of peripheral arterial disease (PAD) was defined as prior lower extremity PAD according to the American College of Cardiology/American Heart Association 2005 guidelines [17].

Measurements

Cranial MRI scans were performed using a 1.5-Tesla MR system (GyroScan Intera 1.5T master; Philips, Best, The Netherlands, or MRT-2001/P3 excelart; Toshiba, Tokyo, Japan). T1- (repetition time 400 ms; echo time 10 ms) and T2-weighted images (repetition time 3500 ms; echo time 90 ms) were obtained in the transverse plane with 7-mm thick sections. SCI was defined as an area of low signal intensity measuring at least 3 mm on T1-weighted images which was also visible as a hyperintense lesion on T2-weighted images, without corresponding symptoms, in accordance with draft clinical guidelines of the Japanese Society for Detection of Asymptomatic Brain Disease [18]. Hyperintense punctuate lesions evident only on T2-weighted images were excluded from the diagnosis of SCI. In each case, SCI was diagnosed by consensus of two neuroradiologists at Tokyo Women's Medical University Hospital.

GFR was estimated using the following modified three-variable equation for Japanese, as recently proposed by the Japanese Society of Nephrology [19]: GFR = $194 \times SCr^{-1.094} \times age^{-0.287}$ [(if female) × 0.739], where SCr = serum creatinine in mg/dl, measured by an enzymatic method. Patients were divided into the following four eGFR categories: eGFR ≥ 90, 60–89, 30–59 and 15–29 ml/min 1.73/m^2, respectively. Classification of albuminuria was based on the American Diabetes Association (ADA) [20] criteria, using the albumin-to-creatinine ratio (ACR) obtained from a first morning urine specimen. Urinary albumin was determined using the latex agglutination method. Subjects were classified into one of the following three categories: normoalbuminuria (ACR < 30 mg/g), microalbuminuria (ACR 30–299 mg/g) and clinical albuminuria (ACR ≥ 300 mg/g). In this study, CKD was defined as the presence of albuminuria (urinary ACR ≥ 30 mg/g) and/or decreased GFR (< 60 ml/min 1.73/m^2).

HbA_{1c} was measured by HPLC (normal range 4.3–5.8%) and total cholesterol and high-density lipoprotein (HDL) cholesterol were determined enzymatically. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation when serum triglyceride (TG) level was < 4.48 mmol/l [21].

Statistical analyses

Data were expressed as percentage, arithmetic mean ± standard deviation (SD) or geometric mean with 95% confidence interval (CI), as appropriate according to data distribution. Triglycerides and ACR were logarithmically transformed because of skewed distributions. To analyse the relationship between SCI and patient characteristics, the χ^2-test was used for categorical data and Student's *t*-test for continuous data. Logistic regression analysis was used to assess the cross-sectional relationship between each CKD manifestation (albuminuria and reduced eGFR) and SCI. The following covariates were incorporated in the analysis: age, gender, duration of diabetes, history of cardiovascular disease, presence of proliferative diabetic retinopathy, smoking status, body mass index (BMI), systolic and diastolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, uric acid, HbA_{1c}, and the use of calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin type 1 receptor blockers, statins and anti-platelet agents.

All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC, USA) version 9.13. A P value < 0.05 was considered to be statistically significant.

Results

Among 1260 T2DM patients who underwent cranial MRI scans between 1 July 2003 and 30 April 2008, 786 patients were considered to have sufficient data to qualify for inclusion. These included 337 women and 449 men, with a mean (± SD) age of 65 ± 11 years (range = 22–92 years). Normoalbuminuria, microalbuminuria and clinical albuminuria were diagnosed in 424, 208 and 154 patients, respectively. Mean eGFR was 68.6 ± 22.8 ml/min 1.73/m^2 (range 16.6–218.7). Prevalence of patients with eGFR < 60 ml/min 1.73/m^2 was 32.9% (n = 259).

SCI was detected in 415 patients (52.8%). Tables 1 and 2 show clinical characteristics and laboratory data, respectively, for patients with and without SCI. Compared with patients without SCI, those with SCI were significantly older and had a longer duration of diabetes, lower BMI and higher systolic blood pressure and pulse pressure. Patients with SCI also were more likely to have atrial fibrillation, diabetic retinopathy and cardiovascular disease, and were more likely to be treated with oral glucose-lowering agents and insulin.

Mean urinary ACR was significantly higher and eGFR was significantly lower in patients with SCI compared with those without SCI, resulting in a higher prevalence of albuminuria and decreased eGFR in patients with SCI than those without SCI (Table 2). As shown in Fig. 1, the prevalence of SCI significantly increased in relation to both the increase in ACR and decrease in eGFR levels. Multiple logistic regression analysis revealed that logarithmically transformed urinary ACR was significantly associated with SCI (Table 3). However, the relationship between eGFR and SCI did not reach statistical significance after adjustment for other covariates including albuminuria (odds ratio per ml/min 1.73/m^2 = 0.99, 95% CI = 0.98–1.00, P = 0.095).

To assess the robustness of the above results, we conducted a subgroup analysis excluding patients with a history of cerebrovascular disease (n = 74). As in the whole cohort, the prevalence of SCI in those patients without cerebrovascular disease (n = 712) also significantly increased as eGFR levels decreased (29.0, 44.1, 67.0 and 70.7 in patients with eGFR ≥ 90, 60–89, 30–59 and 15–29 ml/min 1.73/m^2, respectively). The significant relationship between albuminuria and SCI remained unchanged (odds ratio 1.54, 95% CI 1.21–1.97, P < 0.001) and the association between eGFR and SCI lost statistical significance in the multivariate logistic regression analysis (odds ratio 0.99, 95% CI 0.98–1.00, P = 0.069).

Table 1 Clinical characteristics and concomitant medication in Type 2 diabetic patients with and without silent cerebral infarction

	Without SCI (n = 371)	With SCI (n = 415)	P value*
Age (years)	61 ± 11	69 ± 9	< 0.001
Gender (% male)	58.8	52.8	0.387
Body mass index (kg/m^2)	24.9 ± 4.3	24.2 ± 3.9	0.011
History of CVD (%)	14.6	32.5	< 0.001
Family history of CVD (%)	39.4	46.0	0.061
Current smoker (%)	22.6	17.8	0.108
Atrial fibrillation (%)	2.2	5.3	0.025
Diabetes duration (years)	15 ± 10	17 ± 10	0.004
Systolic blood pressure (mmHg)	133 ± 20	141 ± 21	< 0.001
Diastolic blood pressure (mmHg)	76 ± 12	75 ± 13	0.452
Pulse pressure (mmHg)	56 ± 17	64 ± 18	< 0.001
Proliferative diabetic retinopathy (%)	17.0	30.6	< 0.001
Glucose-lowering agents (%)			
Oral agents	52.0	42.9	0.012
Insulin	43.7	56.9	< 0.001
Anti-hypertensive agents (%)			
Calcium channel blockers	28.3	51.8	< 0.001
ACEIs	15.4	20.0	0.094
ARBs	32.9	55.7	< 0.001
α-blockers	1.6	6.8	< 0.001
β-blockers	8.9	12.1	0.164
Diuretics	3.8	12.3	< 0.001
Anti-platelet agents (%)	31.5	61.2	< 0.001
Statins (%)	30.2	37.4	0.035

Data are expressed as mean ± SD or percentage.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; CVD, cardiovascular disease; SCI, silent cerebral infarction; SD, standard deviation.
*Student's t-test or χ^2-test.

Table 2 Laboratory data in Type 2 diabetic patients with and without silent cerebral infarction

	Without SCI (n = 371)	With SCI (n = 415)	P value*
HbA_{1c} (%)	8.2 ± 1.8	8.0 ± 1.7	0.324
Triglycerides (mmol/l)†	1.4 (1.33–1.49)	1.4 (1.37–1.51)	0.568
HDL cholesterol (mmol/l)	1.3 ± 0.45	1.3 ± 0.41	0.982
LDL cholesterol (mmol/l)	3.0 ± 0.93	3.0 ± 0.91	0.957
Uric acid (μmol/l)	303 ± 83	315 ± 95	0.106
Haemoglobin (g/l)	137 ± 16	129 ± 18	< 0.001
ACR (mg/g)†	26 (22–32)	73 (59–89)	< 0.001
< 30 (%)	65.5	43.9	< 0.001
30–299 (%)	22.6	29.9	0.023
≥ 300 (%)	11.9	26.3	< 0.001
Serum creatinine (μmol/l)	73 ± 28.3	80 ± 38.9	< 0.001
eGFR (ml/min 1.73/m^2)	76 ± 22.2	62 ± 21.8	< 0.001
< 60 (%)	20.1	43.9	< 0.001

Data are expressed as mean ± SD, geometric mean (95% CI) or percentage.
ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL/LDL, high-/low-density lipoprotein; SCI, silent cerebral infarction; SD, standard deviation.
*Student's t-test or χ^2-test.
†Geometric mean.

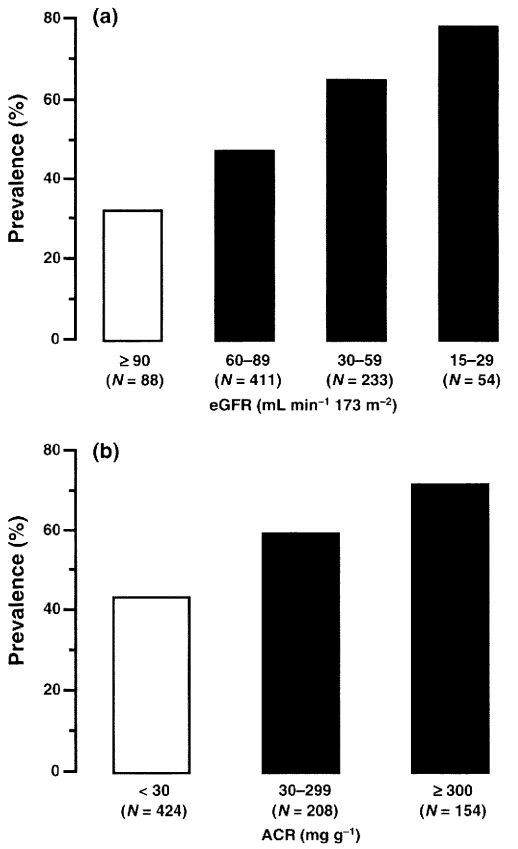

FIGURE 1 Prevalence of silent cerebral infarction in patients with Type 2 diabetes stratified by (a) estimated glomerular filtration rate (eGFR) and (b) urinary albumin-to-creatinine ratio (ACR).

Finally, odds ratios were calculated for six subgroups classified according to eGFR (≥ 60 ml/min 1.73/m^2 or less) and category of albuminuria (normal, microalbuminuria or clinical albuminuria) to determine the simultaneous effect of these two CKD manifestations on the prevalence of SCI (the subgroup with eGFR ≥ 60 ml/min 1.73/m^2 and normoalbuminuria was used as the reference group). As shown in Fig. 2, the impact of reduced eGFR on prevalent SCI was observed only in patients with clinical albuminuria, whereas a stepwise increase in odds ratios was observed with ascending category of albuminuria, regardless of eGFR level.

Table 3 Multiple logistic regression model investigating risk factors for silent cerebral infarction in patients with Type 2 diabetes

	OR	95% CI	P value*
Age (years)	1.09	1.07–1.11	< 0.001
Systolic blood pressure (mmHg)	1.01	1.00–1.02	0.001
Body mass index (kg/m^2)	0.95	0.90–0.99	0.028
Log albumin-to-creatinine ratio (mg/g)	1.89	1.41–2.15	< 0.001
Proliferative diabetic retinopathy (presence vs. absence)	1.78	1.18–2.69	0.006
Anti-platelet agent (presence vs. absence)	2.05	1.45–2.87	0.001

CI, confidence interval; OR, odds ratio.
*Multiple logistic regression analysis (stepwise method).

Discussion

Although CKD is a known risk factor for SCI and stroke, the independent effects of albuminuria and decreased eGFR on SCI have been largely unexplored, particularly in diabetic patients who carry a high risk of developing stroke. Our study in Japanese T2DM patients demonstrates that patients with SCI have a

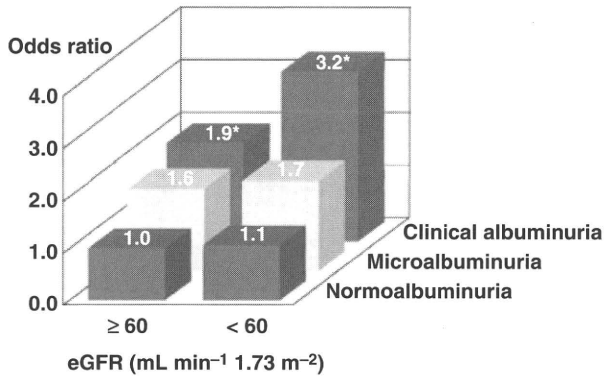

FIGURE 2 Odds ratios of silent cerebral infarction in patients with Type 2 diabetes stratified by eGFR (≥ and < 60 ml min 1.73/m^2) and urinary ACR levels (normoalbuminuria urinary ACR < 30, microalbuminuria 30–299, clinical albuminuria ≥ 300 mg/g). The subgroup with eGFR ≥ 60 ml/min 1.73/m^2 and normoalbuminuria was defined as the reference group. In the multivariate logistic regression analysis with a stepwise selection procedure, the following variables were incorporated as candidates for explanatory variables: age, gender, body mass index, history of cardiovascular disease, smoking status, duration of diabetes, presence of proliferative diabetic retinopathy, systolic blood pressure, diastolic blood pressure, glycated haemoglobin (HbA_{1c}), logarithmically transformed triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, the use of rennin–angiotensin system blockers, anti-platelet agents and statins. *P < 0.05 vs. reference group.

significantly greater prevalence of albuminuria and reduced eGFR than those without SCI. In the univariate analysis, both urinary ACR and eGFR were significantly associated with SCI; however, the association between eGFR and SCI lost statistical significance when assessed in the multivariate analysis. In contrast, albuminuria remained a significant risk factor for SCI, suggesting a potentially causal relationship between albuminuria and risk of SCI in patients with T2DM.

We [5] and others [22] have previously shown that albuminuria and proteinuria are prospectively and independently associated with incident stroke in patients with T2DM. The current study extends this association to cerebral small vessel disease and subclinical stroke in diabetic patients. Albuminuria and cardiovascular disease share numerous risk factors that may explain this relationship, including oxidative stress [23], inflammation [24], endothelial dysfunction [24], obesity [25], thrombotic state [26], hypertension [27] and dyslipidaemia [28]. In addition, similarities between the haemodynamic and anatomical aspects of renal and cerebral small vessel disease [29,30] may help to explain the relationship between albuminuria and SCI in T2DM patients in this study.

Previous studies examining the association between reduced GFR and SCI in a variety of clinical settings have yielded conflicting results. A recent population-based study from the Netherlands [31] demonstrated that reduced GFR was not associated with lacunar infarcts, when adjusted for traditional and non-traditional cardiovascular risk factors. In contrast, a significant association was found between eGFR or alternative measures of GFR, including cystatin C and SCI in both diabetic and non-diabetic individuals [13,32,33]. These studies did not include information on the presence of albuminuria or proteinuria [13,33] or included small number of subjects (n = 51) [32]. Therefore, it is unclear whether the statistical association between reduced GFR and SCI may be confounded by the presence of albuminuria in some patients in these studies. Our study showed that, in T2DM patients, the association between reduced GFR and SCI observed in univariate analysis disappeared when adjusted for covariates including albuminuria. These findings were unchanged when GFR was estimated by the Modification of Diet in Renal Disease (MDRD) formula [34] instead of the Japanese-specific equation [19] (data not shown). Longitudinal studies are needed to establish the independent effects of these renal manifestations on incident SCI.

The importance of diabetes as a risk factor for SCI remains uncertain. In this study, we found the prevalence of SCI was 52.8% in T2DM patients, which was higher than previous population-based studies (8–28%) [33,35–38] but is within the range reported in diabetic patients in previous studies [39]. However, cranial MRIs in this study were mainly performed for the purpose of screening for SCI, which most likely yielded a strong selection bias. Additionally, the higher age (mean 65 years) and inclusion of patients with proliferative diabetic retinopathy, cardiovascular disease or moderate to severe renal dysfunction (CKD stages 3 and 4) may affect the prevalence of SCI in our study. Therefore, the relatively higher prevalence of SCI in this study should be discounted as evidence for an increased risk of SCI in Japanese T2DM patients.

Other limitations of this study may include the ethnic and social homogeneity of the study population (as a result of its being a hospital-based study), cross-sectional study design and dependence upon single measurements for determination of ACR and eGFR. Nevertheless, the study's large sample size and consistent use of first morning specimens for ACR measurement [40] strengthen its potential relevance to clinical practice.

In conclusion, this hospital-based cross-sectional study has demonstrated that increased levels of urinary albumin excretion are closely associated with a higher prevalence of SCI in T2DM patients. Decreased GFR does not appear to show a similar association. A causal relationship between albuminuria and incident SCI remains to be clarified in longitudinal studies.

Competing interests

Nothing to declare.

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ORIGINAL ARTICLE

Silent cerebral infarction is associated with the development and progression of nephropathy in patients with type 2 diabetes

Ryotaro Bouchi, Tetsuya Babazono, Naoshi Yoshida, Izumi Nyumura, Kiwako Toya, Toshihide Hayashi, Ko Hanai, Nobue Tanaka, Akiko Ishii and Yasuhiko Iwamoto

Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease in patients with diabetes. The relationship between renal manifestations of CKD (albuminuria and decreased glomerular filtration rate) and silent cerebral infarction (SCI) has attracted attention; however, most studies examined the effects of components of CKD on prevalence of SCI. We sought to assess the relationship between SCI and the development and progression of nephropathy in type 2 diabetic patients. We studied 366 type 2 diabetic patients with normoalbuminuria (urinary albumin-to-creatinine ratio [ACR] $<30\,mg\,g^{-1}$, *N*=246) or microalbuminuria (ACR=30–299 $mg\,g^{-1}$, *N*=120). SCI was defined by cranial MRI. The primary end point was progression from normo- to microalbuminuria or from micro- to macroalbuminuria. The cumulative incidence of the primary end point was estimated using the Kaplan–Meier method. Risk estimates for reaching the end point were calculated using Cox proportional hazard model analyses. During a median follow-up period of 3.9 years, 23 normoalbuminuric and 24 microalbuminuric patients reached the primary end point. Patients with SCI (*N*=171) had a greater incidence of reaching the end point than those without SCI (*N*=195, *P*=0.020 by the log-rank test), with a hazard ratio of 2.02 (95% confidence interval=1.09–3.72, *P*=0.025) in the multivariate Cox regression model. Although the common pathogenesis of SCI and albuminuria in diabetic patients is still unclear, SCI may be a predictor of progression of nephropathy in type 2 diabetic patients.
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Keywords: albuminuria; diabetic nephropathy; silent cerebral infarction

INTRODUCTION

Chronic kidney disease (CKD)[1] is an independent risk factor for cardiovascular disease in both the general population[2] and diabetic patients.[3] Albuminuria, one of the important components of CKD,[1] has been shown to be associated with incident cardiovascular disease[3,4] and progression of renal impairment.[5] It is, therefore, widely recommended that urinary albumin should be measured not only for the early detection of diabetic nephropathy,[6,7] but also to evaluate the risk of incident cardiovascular disease.

Silent cerebral infarction (SCI), which has a predilection for the subcortical white matter and basal ganglia, is commonly observed on cranial MRI scans in the elderly and hypertensive patients.[8,9] SCI is thought to be a clinical end-organ manifestation of arteriosclerosis in the brain, as well as retinal arterial sclerosis in the eyes and renal sclerosis in the kidneys,[10,11] and the presence of SCI predicts incident clinically evident stroke,[12] cardiovascular disease[13] and dementia.[14] SCI has been also shown to be associated with albuminuria in community-dwelling elderly persons[15] and diabetic patients.[16] We have recently shown that (micro)albuminuria may be a predictor of incident stroke in patients with type 2 diabetes.[17] These studies suggest the organ cross-talk between brain and kidneys. A recent study indicated that SCI may predict progression to end-stage renal failure in patients with type 2 diabetes;[18] however, there is limited understanding of whether patients with SCI are at increased risk of the development and progression of early stage of diabetic nephropathy. We, therefore, sought to determine the potential contribution of SCI to increased risk of development and progression of nephropathy in patients with type 2 diabetes.

METHODS

Study population

This study was conducted in accordance with the Declaration of Helsinki. We recruited consecutive patients with type 2 diabetes, 20 years or older, who underwent cranial MRI at the Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan, during the period between 1 July 2003 and 30 April 2008. As the Japan Brain Dock Society recommends brain MRI scans in high-risk middle-aged or elderly persons (that is those with hypertension or diabetes) (http://www.snh.or.jp/jsbd/pdf/guideline2008.pdf),

Division of Nephrology and Hypertension, Department of Medicine, Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan
Correspondence: Dr T Babazono, Division of Nephrology and Hypertension, Diabetes Center, Tokyo Women's Medical University School of Medicine, 8-1 Kawadacho, Shinjukuku, Tokyo 162-8666, Japan.
E-mail: babazono@dmc.twmu.ac.jp
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