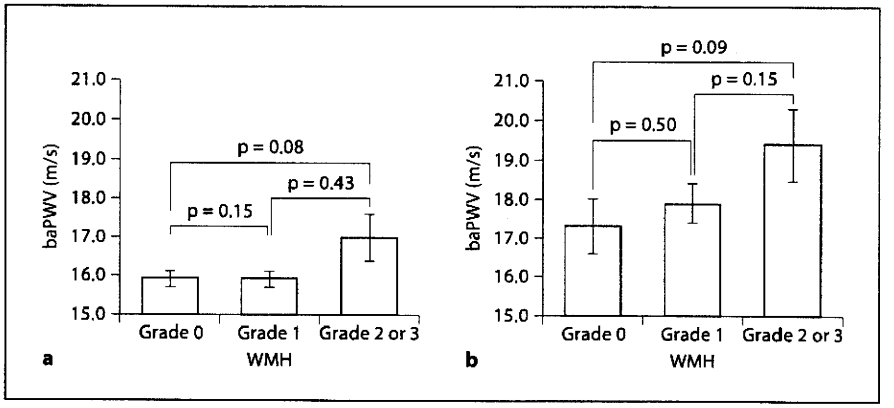

Fig. 2. Multivariate comparison of baPWV among the three groups classified by WMH grade in subjects without lacunar infarcts (**a**) and in subjects with lacunar infarcts (**b**). baPWV was adjusted for age, sex, body mass index, past history of heart disease, total cholesterol, hemoglobin A_{1c}, antihypertensive medication, medication for hyperlipidemia, medication for diabetes mellitus, smoking, alcohol consumption, and 24-hour ambulatory SBP using analysis of covariance.

Table 3. Clinical characteristics of the subjects classified by the presence or absence of SCLs

	SCLs		p
	yes (n = 164)	no (n = 199)	
Age, years	68.5 ± 6.2	63.7 ± 5.7	<0.001
Sex, men/women	47/117	54/145	0.77
BMI, kg/m^2	23.5 ± 3.0	24.3 ± 2.9	0.005
24-hour SBP, mm Hg	123.8 ± 11.2	120.8 ± 11.5	0.01
24-hour DBP, mm Hg	71.9 ± 6.6	71.1 ± 6.8	0.22
24-hour PP, mm Hg	51.9 ± 7.0	49.7 ± 6.9	0.004
24-hour MAP, mm Hg	89.2 ± 7.7	87.6 ± 8.0	0.06
24-hour HR, beats/min	67.6 ± 7.4	68.1 ± 6.4	0.49
baPWV, m/s	17.6 ± 3.4	15.7 ± 2.6	<0.001
Total cholesterol, mg/dl	208.0 ± 31.6	206.7 ± 31.0	0.71
HDL cholesterol, mg/dl	58.5 ± 14.0	57.8 ± 14.9	0.68
Triglycerides, mg/dl	130.2 ± 99.9	137.2 ± 88.3	0.48
HbA_{1c}, %	5.4 ± 0.6	5.3 ± 0.5	0.24
Antihypertensive medication, %	47.0	26.3	<0.001
Medication for diabetes mellitus, %	4.9	0.8	0.07
Medication for hyperlipidemia, %	9.2	7.1	0.47
Past history of heart disease, %	11.0	6.1	0.09
Smoking, %	11.0	8.6	0.44
Alcohol consumption, %	31.1	29.8	0.79

SCLs = Silent cerebrovascular lesions; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; HR = heart rate; baPWV = brachial-ankle pulse wave velocity; HDL = high-density lipoprotein; HbA_{1c} = hemoglobin A_{1c}.

associations were also observed both in subjects with lacunar infarcts and in those without (fig. 2) (interaction p = 0.94). Furthermore, baPWVs were significantly higher in subjects with SCLs than in those without SCLs (17.0 ± 0.2 vs. 16.2 ± 0.2 m/s) (fig. 1c). In contrast, after adjustment there were no significant differences in 24-hour SBP values between individuals with and without lacunar infarcts, among the three groups by WMH grade, and between individuals with and without SCLs.

Table 4 shows the adjusted odds ratios (ORs) and 95% confidence intervals (CI) for lacunar infarcts, WMHs, and SCLs with 24-hour SBP and baPWV. Twenty-four-hour SBP was not a significant determinant for the presence of lacunar infarcts, increased WMH grade and the presence of SCLs except for model 1. On the other hand, baPWV was a determinant for the presence of lacunar infarcts, even including 24-hour SBP as a covariate (model 3). Although the significant association between baPWV and the presence of WMHs or SCLs disappeared in model 3, ORs for the presence of WMHs or SCLs tended to increase with increased baPWV. Compared to the ORs between the intermediate model (model 1) and the fully adjusted model (model 2), the magnitudes of the relationships between SBP/baPWV and lacunar infarct/WMH/SCLs were weakened in the fully adjusted models (table 4). In the fully adjusted models, interaction terms between baPWV and age (interaction p = 0.04) and antihypertensive medication (interaction p = 0.04) were found to be associated with SCLs, indicating that the relationship between baPWV and SCLs was dependent on age and antihypertensive medication.

Table 4. ORs and 95% CI (in parentheses) for lacunar infarct, WMH and SCIs with 24-hour SBP and baPWV

	Lacunar infarct		WMH		SCLs	
	OR	p	OR	p	OR	p
Model 1						
24-hour SBP						
<117 mm Hg	1.00	-	1.00	-	1.00	-
117–127 mm Hg	1.12 (0.58–2-16)	0.75	1.90 (1.07–3.35)	0.03	1.38 (0.79–2.42)	0.26
>127 mm Hg	1.81 (0.96–3.41)	0.07	2.08 (1.18–3.68)	0.01	1.89 (1.08–3.32)	0.03
baPWV						
<14.8 m/s	1.00	-	1.00	-	1.00	-
14.8–17.3 m/s	2.77 (1.35–5.67)	0.005	1.97 (1.10–3.54)	0.02	2.07 (1.17–3.64)	0.01
>17.3 m/s	2.78 (1.34–5.78)	0.006	1.15 (1.10–1.19)	0.01	2.28 (1.27–4.08)	0.006
Model 2						
24-hour SBP						
<117 mm Hg	1.00	-	1.00	-	1.00	-
117–127 mm Hg	0.97 (0.48-1.97)	0.94	1.71 (0.94–3.11)	0.08	1.24 (0.68–2.27)	0.49
>127 mm Hg	1.60 (0.81-3.16)	0.18	1.77 (0.97–3.23)	0.06	1.68 (0.92–3.07)	0.09
baPWV						
<14.8, m/sec	1.00	-	1.00	-	1.00	-
14.8–17.3 m/s	2.46 (1.17-5.14)	0.02	1.74 (0.96–3.15)	0.07	1.81 (1.01–3.26)	0.046
>17.3 m/s	2.36 (1.09-5.12)	0.03	1.98 (1.07–3.67)	0.03	2.00 (1.08–3.70)	0.03
Model 3						
24-hour SBP						
<117 mm Hg	1.00	-	1.00	-	1.00	-
117–127 mm Hg	0.97 (0.38-1.66)	0.54	1.48 (0.79–2.76)	0.22	1.04 (0.55–1.97)	0.90
>127 mm Hg	1.18 (0.57-2.46)	0.66	1.44 (0.75–2.74)	0.27	1.30 (0.67–2.51)	0.44
baPWV						
<14.8 m/s	1.00	-	1.00	-	1.00	-
14.8–17.3 m/s	2.37 (1.10-5.11)	0.03	1.54 (0.83–2.88)	0.18	1.68 (0.91–3.13)	0.10
>17.3 m/s	2.26 (0.99-5.45)	0.053	1.72 (0.89–3.31)	0.11	1.82 (0.94–3.55)	0.07

CI = Confidence interval; WMH = white matter hyperintensity; SCLs = silent cerebrovascular lesions; SBP = systolic blood pressure; baPWV = brachial-ankle pulse wave velocity; OR = odds ratio.

Model 1 was adjusted for age, sex and 24-hour SBP or baPWV. Model 2 was adjusted for age, sex, body mass index, past history of heart disease, total cholesterol, hemoglobin A_{1c}, medication use, smoking, alcohol consumption and 24-hour SBP or baPWV. Model 3 was adjusted for age, sex, body mass index, past history of heart disease, total cholesterol, hemoglobin A_{1c}, medication use, smoking, alcohol consumption, and both 24-hour SBP and baPWV.

Discussion

In the present study, the associations between lacunar infarct, WMH, SCLs and baPWV were explored. Overall, baPWV was significantly associated with the presence of a lacunar infarct, independently of cerebrovascular risk factors, including 24-hour SBP (table 4; fig. 1). baPWV was significantly higher with increasing WMH grade (fig. 1) after adjustment for cerebrovascular risk factors. However, the OR for WMH was not significantly higher in the group with the highest baPWV compared with that in the group with the lowest baPWV (table 4). Henskens et al. [26] previously reported the association between lacunar infarction, WMH and arterial stiffness in 167 hypertensive patients. The association was independent of age, sex, office MAP and office heart rate. The present result provides stronger evidence because 24-hour ambulatory BP was used instead of office BP, and 24-hour ambulatory BP is a better predictor of morbidity and mortality [9–12].

In the present study, baPWV was independently associated with the presence of lacunar infarcts. We have also previously demonstrated that microalbuminuria appears to be associated with baPWV independently of

24-hour SBP and other cardiovascular risk factors [18]. Hoth et al. [27] also suggested that endothelial dysfunction was associated with WMH independently of cardiovascular risk factors. Endothelial dysfunction and arterial stiffness represent different aspects of vascular disease. However, there is certainly some crosstalk between these two pathophysiological processes [28]. The exact mechanism explaining how increased arterial stiffness is associated with microvascular diseases has not been elucidated yet. According to O'Rourke and Safar [29], in vasodilated organs such as the brain and kidney, small vessels are exposed to pulsatile flow and pressure throughout the systole and diastole under normal conditions because of low resistance in these vessels compared with other vascular beds. This anatomical feature in cerebral vessels enables pulsatile flow and pressure to reach the cerebral microvasculature. Although cerebral vessels tolerate these pulsatile flows and pressures, they are susceptible to increased fluctuations of pressure and flow. Increased arterial stiffness augments pulsatile flow and pressure, and pulsatile stress reaches the dilated cerebral vessels and extends more deeply to the microvasculature [30]. The present results might indicate the presence of a process whereby increased arterial stiffness enhances pressure and flow pulsations to the brain, thereby inducing endothelial dysfunction. Therefore, endothelial dysfunction appears to be related to arterial stiffness and SCLs.

In this study, 24-hour SBP was not associated with silent cerebrovascular diseases although several studies have shown that ambulatory BP is closely associated with damage to the target organ. The Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), showed that brachial BP is not always a good surrogate for the effect of BP-lowering drugs on arterial hemodynamics [31]. Furthermore, the ASCOT-CAFE study suggested that central aortic PP may be a determinant of clinical outcomes. An increase in arterial stiffness assessed by PWV augments the second peak of central SBP, and, consequently, central PP, because of early return of the reflected wave to the ascending aorta. Thus, in contrast to brachial BP, PWV may be one of the determinants of central BP, a predictor of clinical outcomes. This may be one of the factors that explain the difference between the association of PWV and that of brachial BP with SCLs.

We evaluated the relationships between SBP/baPWV and lacunar infarct/WMH/SCLs in the intermediate models that adjusted for age and sex and in fully adjusted models that adjusted for body mass index, past history of heart disease, total cholesterol, hemoglobin A_{1c}, medication use, smoking and alcohol consumption, in addition to age and sex. The changes in the ORs in the different models may indicate that hypertension, diabetes and a history of cardiac disease were causes of both arterial stiffness and subclinical cerebrovascular lesions, and might explain the relationships between SBP/baPWV and lacunar infarct/WMH/SCLs.

The present study had some limitations. First, over 30% of the 572 initial subjects with both baPWV and MRI measurements were excluded due to incomplete anthropometric measurements, biomedical tests, 24-hour ambulatory BP monitoring, and medical questionnaires. Although baPWVs did not significantly differ between patients who were included and those who were excluded from this analysis (16.6 ± 3.1 vs. 16.8 ± 3.3 m/s, p = 0.32), subjects who were included in this analysis were younger and more likely to be female and have SCLs than the others (age, 65.8 ± 6.4 vs. 66.8 ± 6.0 years, p = 0.006; female, 27.8 vs. 33.6%, p = 0.04; SCLs, 45.2 vs. 51.8%, p = 0.02). Therefore, this would imply a certain selection bias. Second, blood flow in small cerebral vessels was not measured. Third, because this study was a cross-sectional study, the causal relationship between arterial stiffness and SLCs remains to be elucidated. Prospective studies are necessary to resolve this issue. Fourth, baPWV was used as a measure of aortic stiffness instead of the standard method, i.e. carotid-femoral PWV. baPWV includes information related to peripheral arteries. However, it has been demonstrated that baPWV correlates with carotid-femoral PWV and reflects large-artery stiffness [23]. Finally, although medications for hypertension, diabetes and hyperlipidemia might affect the association between arterial stiffness and SCLs, these associations did not differ after adjustment for these medications. However, we could not evaluate the potential role of medications because we did not have detailed data on medication histories.

In conclusion, this study demonstrated that arterial stiffness was associated with the presence of SLCs independently of traditional cerebrovascular risks, including brachial BP. Although arterial stiffness showed a certain association with WMH, the association was not robust when compared with that between arterial stiffness and lacunar infarction. The results indicate that arterial stiffness may be a strong risk factor or predictor of SLCs, and baPWV measurement will contribute to their early detection.

Acknowledgements

We are grateful to the staff members of the Iwate Prefectural Stroke Registry and to the public health nurses in Ohasama for their valuable support of this project. This work was supported by Grants for Scientific Research (15790293, 16590433, 17790381, 17790381, 18390192, 18590587, 19590929 and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; a Grant-in-Aid [H17-Kenkou-007, H18-Junkankitou (Seishuu)-Ippan-012, and H20-Junkankitou (Seishuu)-Ippan-009, 013] from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; a Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477 and 20.54043), Tokyo, Japan; Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; the Japan Atherosclerosis Prevention Fund; the Uehara Memorial Foundation; the Takeda Medical Research Foundation; National Cardiovascular Research Grants, and Biomedical Innovation Grants.

Disclosure Statement

None.

References

1 Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003;34:1126–1129.
2 Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S: Subcortical silent brain infarction as a risk factor for clinical stroke. Stroke 1997;28:1932–1939.
3 Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215–1222.
4 Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI: Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995;26:485–490.
5 Hashimoto J, Chonan K, Aoki Y, Nishimura T, Ohkubo T, Hozawa A, Suzuki M, Matsubara M, Michimata M, Araki T, Imai Y: Pulse wave velocity and the second derivative of the finger photoplethysmogram in treated hypertensive patients: their relationship and associating factors. J Hypertens 2002;20:2415–2422.
6 Hashimoto J, Watabe D, Kimura A, Takahashi H, Ohkubo T, Totsune K, Imai Y: Determinants of the second derivative of the finger photoplethysmogram and brachial-ankle pulse-wave velocity: the Ohasama study. Am J Hypertens 2005;18:477–485.
7 Sugawara J, Hayashi K, Yokoi T, Cortez-Copper MY, DeVan AE, Anton MA, Tanaka H: Brachial-ankle pulse wave velocity: an index of central arterial stiffness? J Hum Hypertens 2005;19:401–406.
8 Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 2002;25:359–364.
9 Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetière P, Benetos A: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–1241.
10 Blacher J, Guerin A, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434–2439.
11 Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME: Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001;21:2046–2050.
12 Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S: Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002;39:10–15.
13 Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P: Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003;34:1203–1206.
14 Ogawa O, Onuma T, Kubo S, Mitsuhashi N, Muramatsu C, Kawamori R: Brachial-ankle pulse wave velocity and symptomatic cerebral infarction in patients with type 2 diabetes: a cross-sectional study. Cardiovasc Diabetol 2003;2:10–15.
15 Scuteri A, Brancati AM, Gianni W, Assisi G, Volpe M: Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. J Hypertens 2005;23:1211–1216.
16 Hanon O, Haulon S, Lenoir H, Seux ML, Rigaud AS, Safar M, Girerd X, Forette F: Relationship between arterial stiffness and cognitive function in elderly subjects with complaints of memory loss. Stroke 2005;36:2193–2197.
17 Imai Y, Nagai K, Sakuma M, Sakuma H, Nakatsuka H, Satoh H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N, Yabe T, Nishiyama A, Abe K: Ambulatory blood pressure of adults in Ohasama, Japan. Hypertension 1993;22:900–912.
18 Ishikawa T, Hashimoto J, Morito RH, Hanazawa T, Aikawa T, Hara A, Shintani Y, Metoki H, Inoue R, Asayama K, Kikuya M, Ohkubo T, Totsune K, Hoshi H, Satoh H, Imai Y: Association of microalbuminuria with brachial-ankle pulse wave velocity: the Ohasama study. Am J Hypertens 2008;21:413–418.
19 Aono Y, Ohkubo T, Kikuya M, Hara A, Kondo T, Obara T, Metoki H, Inoue R, Asayama K, Shintani Y, Hashimoto J, Totsune K, Hoshi H, Satoh H, Izumi S, Imai Y: Plasma fibrinogen, ambulatory blood pressure, and silent cerebrovascular lesions: the Ohasama study. Arterioscler Thromb Vasc Biol 2007;27:963–968.
20 Otani H, Kikuya M, Hara A, Terata S, Ohkubo T, Kondo T, Hirose T, Obara T, Metoki H, Inoue R, Asayama K, Kanno A, Terawaki H, Nakayama M, Totsune K, Hoshi H, Satoh H, Izumi S, Imai Y: Association of kidney dysfunction with silent lacunar infarcts and white matter hyperintensity in the general population: the Ohasama study. Cerebrovasc Dis 2010;30:43–50.
21 Hara A, Ohkubo T, Kondo T, Kikuya M, Aono Y, Hanawa S, Shioda K, Miyamoto S, Obara T, Metoki H, Inoue R, Asayama K, Hirose T, Totsune K, Hoshi H, Izumi S, Satoh H, Imai Y: Detection of silent cerebrovascular lesions in individuals with 'masked' and 'white-coat' hypertension by home blood pressure measurement: the Ohasama study. J Hypertens 2009;27:1049–1055.
22 Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Rander H, Lechner H: Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43:1683–1689.

23 Munakata M, Ito N, Nunokawa T, Yoshinaga K: Utility of automated brachial ankle pulse wave velocity measurements in hypertensive patients. Am J Hypertens 2003;16:653–657.
24 Imai Y, Abe K, Sasaki S, Minami N, Munakata M, Sekino H, Nihei M, Yoshinaga K: Determination of clinical accuracy and nocturnal blood pressure pattern by new portable device for monitoring indirect ambulatory blood pressure. Am J Hypertens 1990;3:293–301.
25 Association for the Advancement of Medical Instrumentation. American National Standard for Electronic or Automated Sphygmomanometers. Washington, Association for the Advancement of Medical Instrumentation, 1987 (ANSI/AAMI SP10-1987).
26 Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW: Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension 2008;52:1120–1126.
27 Hoth KF, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, Paul RH, Jefferson AL, Haley AP, Cohen RA: Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. Stroke 2007;38:308–312.
28 Anderson TJ: Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. Can J Cardiol 2006;22(suppl B):72B–80B.
29 O'Rourke MF, Safar ME: Relationship between aortic stiffening and microvascular disease in brain and kidney. Hypertension 2005;46:200–204.
30 O'Rourke MF, Hashimoto J: Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007;50:1–13.
31 Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H: Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213–1225.

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Brief report

New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study

Makoto Watanabe[a,*], *Yoshihiro Kokubo*[a], *Aya Higashiyama*[a], *Yuu Ono*[a], *Akira Okayama*[a,b], *Tomonori Okamura*[a]

[a] *Department of Preventive Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565, Japan*
[b] *The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 15 July 2009
Received in revised form
12 January 2010
Accepted 18 January 2010
Published on line 10 February 2010

Keywords:
Hemoglobin A1c
Diagnosis criteria
Macro-vascular complications
Cohort study
Japanese

ABSTRACT

The association of the new diagnosis criteria for diabetes adopting hemoglobin A1c, recently proposed by the international expert committee, with macro-vascular complications was tested in a 12-year population-based cohort. The present analysis suggested that this new criteria were applicable to macro-vascular complications in the Japanese.

1. Introduction

Recently, an international expert committee proposed the new diagnosis criteria for diabetes with hemoglobin A1c (HbA1c) mainly on the basis of the relation of HbA1c with micro-vascular complications [1]. It would be also important to estimate the association of HbA1c with macro-vascular complications, although they are not specific to diabetes. Since these new criteria are worldwide, evidence for macro-vascular complications would be needed from diverse populations. Several population-based studies chiefly in the Western have investigated the association of HbA1c with macro-vascular complications [2–5], but there have been few reports from other areas including Asia [6,7]. Therefore, we tested the association of the new proposed criteria of HbA1c with macro-vascular complications in a 12-year cohort study in a Japanese urban area where incidence of strokes was higher than myocardial infarction (MI) [8].

* *Corresponding author.* Tel.: +81 6 6833 5012x2186; fax: +81 6 6833 5300.
E-mail address: makotow@hsp.ncvc.go.jp (M. Watanabe).
0168-8227/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2010.01.019

2. Materials and methods

The details of the Suita study have been described elsewhere [9–11]. Briefly, the Suita study is a population-based cohort study in a Japanese urban area. From the Suita city residents, 6406 men and women (aged 30–79 years) were randomly sampled and participated in a baseline survey from September 1989 to March 1994, and were followed up to December 2005. The individuals with a history of MIs or strokes were excluded at enrollment. Informed consent was obtained from all subjects, and this study was approved by the institutional review board at the National Cardiovascular Center.

In the enrollment period, HbA1c measurements were conducted from June 1990 to February 1991. The present analysis was conducted in 1607 initially healthy subjects (764 men and 843 women, mean age: 51.2 years) who had HbA1c measurements at baseline.

A baseline survey included questionnaires, anthropometric measurements, or fasting blood sample tests. All blood samples were analyzed immediately after blood sampling by an automatic analyzer at the laboratory of the National Cardiovascular Center. HbA1c was measured by the high performance liquid chromatography method (coefficient of variance was 1.5%). It was known that HbA1c values in Japan were lower than those mainly in the United States which adopted the National Glycohemoglobin Standardization Program (NGSP) method [12]. Converting formula from the HbA1c values by the Japan Diabetes Society (JDS) method to the ones by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method was as follows; IFCC value (mmol/mol) = 10.39 × JDS value (%) − 16.8 [12]. Converting formula from the HbA1c values by the IFCC method to the ones by the NGSP method was as follows; NGSP value (%) = 0.0981 × IFCC value (mmol/mol) + 1.95 [12]. All present analysis adopted the HbA1c values by the NGSP method.

To detect MI or stroke events, each subject was checked by physicians or nurses at clinical visits every 2 years. In addition, yearly questionnaires by mail or telephone were completed for all participants. We also reviewed in-hospital medical records. MIs were defined according to the criteria by the MONICA project [13]. Strokes were defined according to the National Survey of Stroke criteria [14]. Death certificates were also searched systematically to complete surveillance for fatal strokes and MIs.

HbA1c levels were divided into 3 categories according to the proposed new criteria (i.e., ≤5.9%, 6.0–6.4%, ≥6.5%) to calculate crude incidence rates (per 1000 person-years), or estimate age- and multivariate-adjusted hazard ratios (HRs) by subtypes of cardiovascular diseases (CVD) (all CVDs, MIs, all strokes, ischemic strokes). HRs with confidence intervals (CIs) were estimated using a Cox regression model. The multivariate-adjusted model adjusted for age, sex, body mass index, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication), use of antidiabetic medication, hypercholesterolemia (total cholesterol ≥5.7 mmol/L or use of antihypercholesterolemic medication), current cigarette use, and current alcohol consumption at baseline. The P values for trend (2-tailed) were calculated to test for linearity of HRs.

Table 1 – Baseline characteristics in a cohort study of a Japanese urban area, 1989–2005.

Number of subjects	1607
Sex (men/women)	764/843
Age (years)	51.2 (11.9)
Body mass index (kg/m^2)	22.5 (3.0)
Hemoglobin A1c (%)	5.3 (0.7)
Hypertension (%)[a]	25.8
Hypercholesterolemia (%)[b]	38.9
Use of antidiabetic medication (%)	0.9
Cigarette use	
Non (%)	54.8
Past (%)	12.6
Current (%)	32.6
Alcohol consumption	
Non (%)	42.3
Past (%)	1.4
Current (%)	56.3

Averages in continuous variables are shown with standard deviation in parentheses.

[a] Hypertension was defined by systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication.

[b] Hypercholesterolemia was defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or use of antihypercholesterolemic medication.

3. Results

The mean follow-up duration was 12.7 years, and 70 cases of CVDs were observed; 24 MIs, 44 strokes (19 hemorrhagic, 22 ischemic, 3 unclassified), and 2 sudden deaths.

Baseline characteristics were demonstrated in Table 1. The average of HbA1c levels was 5.3%, and current cigarette use was 32.6%. Use of antidiabetic medication was 0.9%.

Age- and multivariate-adjusted HRs by HbA1c levels are shown in Table 2. Regardless of subtype of CVDs, a graded increase in crude incidence rates was observed. Age- and multivariate-adjusted HRs for all CVDs, all strokes and ischemic strokes increased linearly with increases in HbA1c, and the multivariate-adjusted HRs in subjects with HbA1c of 6.5% or more were 3.0 (95% CI 1.2–7.4), 3.4 (95% CI 1.1–10.8), 6.4 (95% CI 1.4–30.4), respectively. In the relation between HbA1c and MIs, a significant graded increase in the adjusted HRs was not observed although the HRs were higher in HbA1c of 6.5% or more than that of 5.9% or less.

4. Discussion

The present study in Japan demonstrated that risks for all CVDs or strokes, especially for ischemic strokes, increased with increases in HbA1c levels, and were clearly higher in subjects with HbA1c levels of 6.5% or more. With regard to MIs, graded increase in the HRs was not observed. The results for MIs may be due to the fact that the incidence of MIs is considerably lower than strokes in the Japanese [8]. However, from the view point of prevention of macrovascular complications, defining HbA1c of 6.5% as a cut-off

Table 2 – Incident rates and adjusted HRs with 95% CIs for cardiovascular diseases by HbA1c levels in a cohort study of the Japanese men and women, 1989–2005.

HbA1c levels	N	Number of events	Person-years	Crude incidence rates (per 1000 person-years)	Age-adjusted		Multivariate-adjusted[a]	
					HRs	95%CIs	HRs	95%CIs
All cardiovascular diseases								
≤5.9	1451	54	18627	2.9	1	(reference)	1	(reference)
6.0–6.4	108	9	1289	7.0	1.5	(0.7–3.0)	1.2	(0.6–2.5)
≥6.5	48	7	479	14.6	3.5	(1.6–7.7)	3.0	(1.2–7.4)
					Trend P = 0.003		Trend P = 0.04	
Myocardial infarctions								
≤5.9	1451	20	18627	1.1	1	(reference)	1	(reference)
6.0–6.4	108	2	1289	1.6	0.9	(0.2–3.9)	0.8	(0.2–3.3)
≥6.5	48	2	479	4.2	2.8	(0.6–11.9)	2.5	(0.5–11.6)
					Trend P = 0.32		Trend P = 0.48	
All strokes								
≤5.9	1451	32	18627	1.7	1	(reference)	1	(reference)
6.0–6.4	108	7	1289	5.4	1.9	(0.8–4.3)	1.5	(0.7–3.6)
≥6.5	48	5	479	10.4	4.2	(1.6–10.8)	3.4	(1.1–10.8)
					Trend P = 0.002		Trend P = 0.03	
Ischemic strokes								
≤5.9	1451	15	18627	0.8	1	(reference)	1	(reference)
6.0–6.4	108	4	1289	3.1	2.2	(0.7–6.5)	1.6	(0.5–4.9)
≥6.5	48	3	479	6.3	5.2	(1.5–18.1)	6.4	(1.4–30.4)
					Trend P = 0.006		Trend P = 0.03	

[a] Multivariate-adjusted HRs adjusted for age, sex, body mass index, hypertension, use of antidiabetic medication, hypercholesterolemia, current cigarette use and current alcohol consumption.

point for diabetes seemed to be reasonable in this Japanese population. The international expert committee of the new criteria also recommended that individuals with HbA1c levels of 6.0–6.4% should receive effective preventive intervention [1]. The present analysis demonstrated a graded risk increase in CVDs with HbA1c, so this recommendation also seemed to be applicable to macro-vascular complications.

Recently Kilpatrick et al. pointed the problem that anemias or hemoglobinopathies influenced on HbA1c levels and might give misleading results [15]. Present dataset included hemoglobin concentration and current treatment status for any anemia, although it did not include information for hemoglobinopathies. Prevalence of subjects with hemoglobin levels of less than 11.0 g/dl or on treatment for anemia was only 2.7% in total. In addition, excluding such anemic subjects from the analysis or adjusting for hemoglobin levels in the multivariate analysis hardly altered the results. Accordingly, we think anemias did not influence on present results so much, although present results could not be applied to individuals with anemia or hemoglobinopathies, considering lack of the reliability in HbA1c levels.

There were several limitations in this analysis. First, compared to the whole cohort, the number of samples was considerably smaller. However, since study subjects were determined only by timing of enrollment to the baseline survey, not by arbitrary reasons, this would not bias the results. Second, the single HbA1c measurement at baseline may have underestimated the relationship due to regression dilution bias [16].

In conclusion, the present results suggested that the new worldwide diagnosis criteria for diabetes with HbA1c were applicable to macro-vascular complications in the Japanese population. However, since the present study was conducted in a limited Japanese population, these new criteria should be tested further in various populations.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

We would like to express our gratitude to all members of the Suita City Health Center and the Suita Medical Association. We also thank all researchers and the staffs of the Division of Preventive Cardiology for performing medical examinations and the follow-up. We also thank Satsuki-Junyukai, the volunteers for the administration of the Suita study.

Grant support: This work was supported by grant-in-aids from the Japanese Ministry of Health, Labor and Welfare (H20-SeiShu-013 and H19-SeiShu-021); and the Research Grant for Cardiovascular Disease from the Ministry of Health, Labor and Welfare (20K-6 and 21S-1).

REFERENCES

[1] The International Expert Committee, International expert committee report on the role of the A1c assay in the diagnosis of diabetes, Diab. Care 32 (2009) 1–8.

[2] E. Selvin, J. Coresh, S.H. Golden, F.L. Brancati, A.R. Folsom, M.W. Steffes, Glycemic control and coronary heart disease risk in persons with and without diabetes. The atherosclerosis risk in communities study, Arch. Int. Med. 165 (2005) 1910–1916.

[3] E. Selvin, J. Coresh, E. Shahar, L. Zhang, M. Steffes, A.R. Sharrett, Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the atherosclerosis risk in communities (ARIC) study, Lancet Neurol. 4 (2005) 821–826.

[4] P.K. Myint, S. Sinha, N.J. Wareham, S.A. Bingham, R.N. Luben, A.A. Welch, et al., Glycated hemoglobin and risk of stroke in people without known diabetes in the European prospective investigation into cancer (EPIC)-Norfolk prospective population study: a threshold relationship? Stroke 38 (2007) 271–275.

[5] D.A. Lawlor, A. Fraser, S. Ebrahim, G. Davey Smith, Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women, PLoS Med. 4 (2007) e263.

[6] K. Sunaga, K. Miura, Y. Naruse, M. Sakurai, Y. Morikawa, Y. Kurosawa, et al., Glycated hemoglobin and risk of stroke, ischemic and hemorrhagic, in Japanese men and women, Cerebrovasc. Dis. 26 (2008) 310–316.

[7] S. Nakanishi, M. Yamada, N. Hattori, G. Suzuki, Relationship between HbA1c and mortality in a Japanese population, Diabetologia 48 (2005) 230–234.

[8] H. Ueshima, A. Sekikawa, K. Miura, T.C. Turin, N. Takashima, Y. Kita, et al., Cardiovascular disease and risk factors in Asia: a selected review, Circulation 118 (2008) 2702–2709.

[9] Y. Kokubo, K. Kamide, T. Okamura, M. Watanabe, A. Higashiyama, K. Kawanishi, et al., Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study, Hypertension 52 (2008) 652–659.

[10] T. Okamura, Y. Kokubo, M. Watanabe, A. Higashiyama, Y. Miyamoto, Y. Yoshimasa, et al., Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study, Atherosclerosis 203 (2009) 587–592.

[11] M. Watanabe, T. Okamura, Y. Kokubo, A. Higashiyama, A. Okayama, Elevated serum creatine kinase predicts first-ever myocardial infarction: a 12-year population-based cohort study in Japan, the Suita study, Int. J. Epidemiol. 38 (2009) 1571–1579.

[12] Committee on Diabetes Mellitus Indices, Japan Society of Clinical Chemistry (Chair: Izumi Takei), Japanese guideline for reporting HbA1c results reported in IFCC units and JDS units. *Rinsho Kagaku* 37 (2008):393–409, (Japanese).

[13] H. Tunstall-Pedoe, K. Kuulasmaa, P. Amouyel, D. Arveiler, A.M. Rajakangas, A. Pajak, Myocardial infarction and coronary deaths in the World Health Organization MONICA project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents, Circulation 90 (1994) 583–612.

[14] A.E. Walker, M. Robins, F.D. Weinfeld, The national survey of stroke. Clinical findings, Stroke 12 (1981) I13–44.

[15] E. Kilpatrick, Z. Bloomgarden, P. Zimmet, Is haemoglobin A1c a step forward for diagnosing diabetes? BMJ 339 (2009) b4432.

[16] S. MacMahon, R. Peto, J. Cutler, R. Collins, P. Sorlie, J. Neaton, et al., Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias, Lancet 335 (1990) 765–774.

Hypertension Research (2010) 33, 1238–1243

www.nature.com/hr

ORIGINAL ARTICLE

The combined impact of blood pressure category and glucose abnormality on the incidence of cardiovascular diseases in a Japanese urban cohort: the Suita Study

Yoshihiro Kokubo[1], Tomonori Okamura[1], Makoto Watanabe[1], Aya Higashiyama[1], Yuu Ono[1], Yoshihiro Miyamoto[2], Yoko Furukawa[1,3], Kei Kamide[4,5], Katsuyuki Kawanishi[6], Akira Okayama[7] and Yasunao Yoshimasa[2]

Few prospective studies have examined the combined impact of blood pressure (BP) categories and glucose abnormalities on the incidence of cardiovascular disease (CVD) in the general Asian population. This study aimed to examine the effect of the combined risks of these factors on the incidence of CVD in a general Japanese population. We studied 5321 Japanese individuals (aged 30–79 years), without CVD at baseline, who received follow-up for an average of 11.7 years. Serum fasting glucose categories were defined according to the 2003 American Diabetes Association recommendations. BP categories were defined by the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension. The Cox proportional hazard ratios (HRs) for CVD according to the serum glucose and BP categories were calculated. In 62 036 person-years of follow-up, we documented 364 CVD events (198 stroke and 166 coronary heart disease (CHD)). Compared with normoglycemic subjects, the multivariable HRs (95% confidence intervals (CIs)) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively, in individuals with impaired fasting glucose (IFG), whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively, in individuals with diabetes mellitus (DM). Compared with normoglycemic and optimal blood pressure (BP) subjects, increased risks of CVD were observed in the normoglycemic subjects with high-normal BP or hypertension, the IFG subjects with normal or higher BP, and the DM subjects regardless of BP category (*P*-value for interaction=0.046). In conclusion, the high-normal BP subjects in all glucose categories and the normal BP subjects with IFG showed increased risk of CVD in this Japanese population. Further investigation of larger cohorts of DM subjects should be conducted to better understand this phenomenon.
Hypertension Research (2010) **33**, 1238–1243; doi:10.1038/hr.2010.174; published online 7 October 2010

Keywords: blood pressure category; cardiovascular disease; cohort study; diabetes mellitus; impaired fasting glucose

INTRODUCTION

Hypertension is one of the strongest risk factors for increased incidence of cardiovascular disease (CVD) worldwide.[1–3] Recently, high-normal blood pressure (BP)[1,2] and prehypertension[3] have also been recognized as risk factors for CVD.[4–6] Increased BP is the most likely precipitator of CVD and stroke.[5,7,8] Furthermore, the prevalence of glucose intolerance and obesity has increased greatly in recent years.[9,10] Diabetes mellitus (DM) has become a major public health problem[11,12] as well as a risk factor for all-cause mortality[11] and CVD.[10,13–15] Recently, prediabetic hyperglycemia has been recognized to confer an increased risk for CVD.[16] However, a few population studies[17] have reported a positive association between CVD and impaired fasting glucose (defined as blood glucose of 5.6–6.9 mmol l^{-1} according to the 2003 American Diabetes Association definition).[18]

Evaluation of the combined impact of these two major borderline risk factors is essential in preventing CVD because elevated BP is the highest population attributable fraction (PAF) of CVD incidence, and the incidence of hyperglycemia is increasing in Asian and Western countries. There have been a few population studies on the association between the occurrence of hypertension together with DM and the risk of stroke[19–21] and coronary heart disease (CHD).[22] However, few population cohort studies have evaluated the impact of the combination of BP categories (optimal BP, normal BP, high-normal BP (or prehypertension) and hypertension) and fasting glucose categories (normoglycemia, impaired fasting glucose (IFG) and DM) on the risk

[1]Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan; [2]Department of Atherosclerosis and Diabetes, National Cerebral and Cardiovascular Center, Osaka, Japan; [3]Graduate School of Humanities and Sciences, Nara Women's University, Nara, Japan; [4]Division of Hypertension and Nephrology, National Cerebral and Cardiovascular Center, Osaka, Japan; [5]Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Osaka, Japan; [6]The Suita Medical Association, Osaka, Japan and [7]Japan Anti-Tuberculosis Association, Tokyo, Japan
Correspondence: Dr Y Kokubo, Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan.
E-mail: ykokubo@hsp.ncvc.go.jp
Received 1 April 2010; revised 7 May 2010; accepted 27 June 2010; published online 7 October 2010

of CVD. Thus, the aim of this study was to examine the combined impact of BP categories and blood glucose abnormalities on the incidence of CVD in a general urban Japanese population.

METHODS

Study subjects

The Suita Study, a cohort study for CVD in urban residents, was established in 1989. The details of this study have been described elsewhere.[5,23–29] Briefly, 6485 individuals (aged 30 to 79 years) underwent regular health checkups between September 1989 and March 1994. Some cohort members were excluded for the following reasons: past or present history of CVD at baseline (n=208); missing data (n=170); nonfasting blood collections (n=173); or lost from follow-up (n=613). After applying these exclusions, a total of 5321 subjects (aged 30 to 79 years) participated in the baseline examination. Informed consent was obtained from all participants. This study was approved by the institutional review board of the National Cardiovascular Center.

Measurement of BP and fasting glucose

Measurement of BP has been described elsewhere.[5] In brief, well-trained physicians measured the BP of each individual three times in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 min. Systolic (SBP) and diastolic (DBP) blood pressures were recorded as the average of the second and third measurements, which were taken more than 1 min apart.

At the time of the baseline examination, subjects were classified into one of the following BP categories based on the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension:[2] optimal BP (SBP, $<$120 mm Hg and DBP, $<$80 mm Hg); normal BP (SBP, 120 to 129 mm Hg and DBP, 80 to 84 mm Hg); high-normal BP (SBP, 130 to 139 mm Hg and DBP, 85 to 89 mm Hg); and hypertension (SBP, $\geqslant$140 mm Hg or DBP, $\geqslant$90 mm Hg or antihypertensive drug use). If the SBP and DBP readings for a subject were in different categories, then the subject was categorized into the higher of the two categories.

We performed routine fasting blood collection and immediately measured serum glucose and total cholesterol levels using the same autoanalyzer (Toshiba TBA-80, Toshiba, Tokyo, Japan). Fasting serum glucose categories were defined as follows:[18] DM (fasting serum glucose $\geqslant$7.0 mmol l^{-1} (126 mg per 100 ml) or medications for DM); IFG (fasting serum glucose levels 5.6 to 6.9 mmol l^{-1} (100 to 125 mg per 100 ml)); and normoglycemia (fasting serum glucose levels $<$5.6 mmol l^{-1} ($<$100 mg per 100 ml)). Hypercholesterolemia was defined as total serum cholesterol levels $\geqslant$5.7 mmol l^{-1} (220 mg per 100 ml) or current use of antihyperlipidemic medications. Physicians or nurses administered questionnaires addressing personal habits and present illness at the baseline examination. Body mass index was calculated as weight (kg) divided by height (m) squared.

Confirmation of stroke and coronary heart disease and end point determination

Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the US National Survey of Stroke criteria.[30] For each stroke subtype (that is, cerebral infarction (thrombotic or embolic infarction), intracerebral hemorrhage and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images or autopsies. Definite and probable myocardial infarctions were defined according to the criteria set out by the MONICA project.[31] The criteria for a diagnosis of CHD included first ever acute myocardial infarction, sudden cardiac death within 24 h after the onset of acute illness or coronary artery disease followed by coronary artery bypass surgery or angioplasty. In this study, CVD was defined as stroke or CHD.

To detect CHD and stroke occurrences, each participant's health status was checked during clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed by all participants. In addition, to complete our surveillance for fatal strokes and CHD, we conducted a systematic search for death certificates. All data were checked against medical records to confirm the incidence of CVD. When informed consent could not be obtained for a medical records survey (19.5%), we identified possible strokes or CHD using information from (1) questionnaires for present illness of stroke and CHD at the health examination and/or (2) death certificates bearing a diagnosis of probable stroke or CHD. The end point of the follow-up period for each participant was, whichever of the following options occurred first: (1) date of the first diagnosis of CHD or stroke event; (2) date of death; (3) date of leaving Suita; or (4) 31 December, 2005.

Statistical analysis

Analyses of variance and χ^2-tests were used to compare mean values and frequencies. The Cox proportional hazard ratios (HRs) and 95% confidence intervals (95% CIs) were fitted to each glucose category (normoglycemia, IFG and DM) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at baseline, including BP category (optimal, normal, and high-normal BP and hypertension), hypercholesterolemia (positive or negative), body mass index (continuous variable), smoking status (never, ex-smoker and current smoker) and drinking status (never, ex-drinker and current drinker). Test for effect modification by glucose category was conducted with an interaction term generated by multiplying BP category by glucose category. We conducted tests for trend across the BP categories and tested the significance of this variable.

To express the combined impact of glucose and BP categories on the incidence of CVD in these participants, we estimated the PAF as follows:

$$PAF = Pe \times (HR - 1)/HR,$$

where Pe is the proportion of incident cases in the combination of glucose and BP categories, and HR is the multivariable-adjusted hazard ratio.[32] All statistical analyses were conducted using the SAS statistical software package (release version 8.2; SAS Institute, Cary, NC, USA).

RESULTS

The frequencies of IFG and DM increased with age in both men and women (Figure 1). Table 1 shows the distribution of CVD risk factors at baseline according to fasting glucose categories at baseline. Both men and women with DM were older and had a higher body mass index as well as a higher prevalence of hypertension, hypercholesterolemia and medication for hypertension than those without DM. Men with DM had a lower frequency of never drinking than men without DM.

In 62 036 person-years of follow-up (an average of 11.7 years of follow-up), we documented 364 CVD (198 strokes and 166 CHD) events. Table 2 shows the age- and sex-adjusted HRs and multivariable-adjusted HRs for incidence of CVD according to glucose categories in men and women. Compared with normoglycemic subjects, the multivariable HRs (95% CIs) for CVD, CHD and stroke were 1.25 (1.00–1.58), 1.46 (1.04–2.04) and 1.11 (0.81–1.52), respectively in IFG subjects, whereas these values were 2.13 (1.50–3.03), 2.28 (1.34–3.88) and 2.08 (1.29–3.35), respectively in DM subjects. Compared with normoglycemic subjects, IFG and DM were risk factors for CVD and CHD in women, and DM was a risk factor for CVD and stroke in men.

Figure 2 shows the multivariable HRs of CVD for the combined impact of the fasting glucose and BP categories. Compared with normoglycemic subjects with optimal BP, the following groups showed increased risk of CVD: the normoglycemic subjects with high-normal BP or hypertension (P-value for trend of BP category$<$0.001); the IFG subjects with normal or higher BP (P-value for trend of BP category=0.001); and the DM subjects in any BP category (P-value for trend of BP category=0.41). After excluding subjects taking diabetic medication, the P-value for the BP category trend was not statistically significant in the DM subjects.

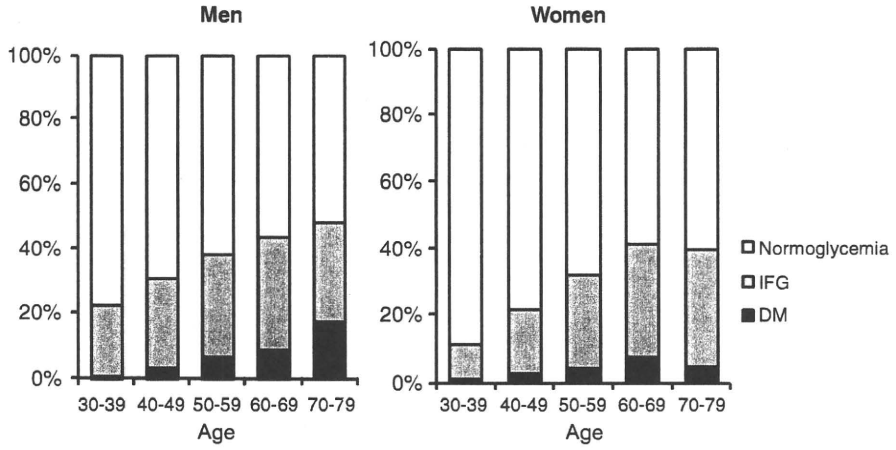

Figure 1 Frequency of type 2 diabetes mellitus according to sex and age.

Table 1 Baseline characteristics of study subjects according to fasting glucose categories at baseline

	Men				*Women*			
	Normoglycemia	*IFG*	*DM*	P-*value*	*Normoglycemia*	*IFG*	*DM*	P-*value*
Number of subjects, *n*	1458	874	154	—	2126	611	98	—
Age, in years	54±14	57±12	60±10	<0.001	52±13	59±11	60±10	<0.001
Body mass index, kg m^{-2}	22.5±2.8	23.3±2.9	23.3±3.2	<0.001	21.8±3.0	23.1±3.4	24.5±4.2	<0.001
Blood pressure category, %[a]				<0.001				<0.001
Optimal blood pressure	37	24	20		49	23	17	
Normal blood pressure	19	19	17		16	16	17	
High-normal blood pressure	16	19	14		13	18	15	
Hypertension	28	39	49		21	43	51	
Hypercholesterolemia, %[b]	26	33	36	<0.001	38	54	59	<0.001
Medication, %								
Hypertension	10	12	18	0.002	8	16	22	<0.001
Diabetes	—	—	36	—	—	—	38	—
Smoking status, %				0.156				0.325
Current	55	51	50		13	10	11	
Quit	25	29	32		3	3	4	
Never	19	20	18		84	87	85	
Drinking status, %				<0.001				0.330
Current	76	77	76		34	32	24	
Quit	2	2	9		1	1	2	
Never	22	20	15		65	67	74	

Abbreviations: DM, diabetes mellitus; DBP, diastolic blood pressure; IFG, impaired fasting glucose; SBP, systolic blood pressure.
Normoglycemia: fasting glucose levels <5.6 mmol l^{-1}; IFG: fasting glucose levels 5.6 to 6.9 mmol l^{-1}; DM: fasting glucose levels ⩾7.0 mmol l^{-1} or medication for diabetes.
[a]Blood pressure category was based on the ESH–ESC 2007 guidelines: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal blood pressure (SBP 120–129 mm Hg and DBP 80–84 mm Hg), high-normal blood pressure (SBP 130–139 mm Hg and DBP 85–89 mm Hg) and hypertension (SBP ⩾140 mm Hg or DBP ⩾90 mm Hg or antihypertensive drug use).
[b]Hypercholesterolemia: antilipidemic drug user or total cholesterol ⩾5.7 mmol l^{-1} ± values are the means±s.d.'s.

The significant interaction terms between fasting blood glucose and BP categories were observed in CVD (P=0.046); however, the interaction term was not significant after exclusion of DM subjects.

Using the HRs, we estimated the PAF for CVD to exposure to the combined impact of fasting glucose and BP categories at baseline (Figure 3). The population-attributable risk percentage for CVD incidence was estimated at 3.7% for subjects with normoglycemia and high-normal BP, 5.7% for subjects with IFG and normal or high-normal BP group and 8.2% for subjects with DM and any BP category group, when comparing these groups with the normoglycemic and optimal BP group.

DISCUSSION

In this population cohort study, we found that DM was a risk factor for CVD, stroke and CHD, whereas an IFG of 5.6 to 6.9 mmol l^{-1} was a risk factor for CVD and CHD only. A combined effect of IFG

Table 2 Age- and multivariable-adjusted hazard ratios (95% confidential intervals) for cardiovascular disease according to blood glucose category

	Blood glucose category			
	Normoglycemia	*IFG*	*Diabetes*	*P-value for trend*
Men and women, number	3584	1485	252	
Person-years, in years	42 701	16 741	2594	
Cardiovascular disease				
Case	184	139	41	
Age and sex-adjusted	1	1.34 (1.07–1.68)	2.45 (1.73–3.45)	<0.001
Multivariable-adjusted	1	1.25 (1.00–1.58)	2.13 (1.50–3.03)	<0.001
Coronary artery disease				
Case	78	70	18	
Age and sex-adjusted	1	1.54 (1.10–2.13)	2.53 (1.51–4.25)	<0.001
Multivariable-adjusted	1	1.46 (1.04–2.04)	2.28 (1.34–3.88)	0.001
Stroke				
Case	106	69	23	
Age and sex-adjusted	1	1.21 (0.89–1.65)	2.51 (1.58–3.96)	<0.001
Multivariable-adjusted	1	1.11 (0.81–1.52)	2.08 (1.29–3.35)	0.016
Men, number	1,458	874	154	
Person-years, years	16,901	9844	1560	
Cardiovascular disease				
Case	107	91	25	
Age-adjusted	1	1.19 (0.90–1.58)	1.93 (1.25–2.99)	0.007
Multivariable-adjusted	1	1.13 (0.85–1.51)	1.75 (1.12–2.73)	0.032
Coronary artery disease				
Case	50	50	11	
Age-adjusted	1	1.39 (0.93–2.06)	1.89 (0.98–3.64)	0.027
Multivariable-adjusted	1	1.31 (0.87–1.96)	1.69 (0.86–3.31)	0.077
Stroke				
Case	57	41	14	
Age-adjusted	1	1.01 (0.68–1.52)	2.00 (1.11–3.61)	0.103
Multivariable-adjusted	1	0.97 (0.64–1.46)	1.78 (1.00–3.12)	0.216
Women, number	2,126	611	98	
Person-years, in years	25,800	6897	1033	
Cardiovascular disease				
Case	77	48	16	
Age-adjusted	1	1.62 (1.12–2.33)	3.70 (2.14–6.40)	<0.001
Multivariable-adjusted	1	1.49 (1.02–2.16)	3.07 (1.73–5.45)	<0.001
Coronary artery disease				
Case	28	20	7	
Age-adjusted	1	1.86 (1.04–3.25)	4.62 (1.99–10.72)	<0.001
Multivariable-adjusted	1	1.83 (1.01–3.32)	4.32 (1.81–10.31)	<0.001
Stroke				
Case	49	28	9	
Age-adjusted	1	1.53 (0.96–2.45)	3.54 (1.71–7.29)	<0.001
Multivariable-adjusted	1	1.36 (0.84–2.19)	2.66 (1.22–5.80)	0.018

Abbreviations: DM, diabetes mellitus; IFG, impaired fasting glucose.
Multivariate analyses were adjusted for age, body mass index, hypertension, hyperlipidemia and smoking and drinking status.
Blood glucose categories: Normal, fasting glucose levels $<5.6\,mmol\,l^{-1}$; IFG, fasting glucose levels $5.6–6.9\,mmol\,l^{-1}$; DM, fasting glucose levels $\geq 7.0\,mmol\,l^{-1}$ or medication for diabetes.

and prehypertension on the incidence of CVD was observed. The high-normal BP subjects in any glucose category and the normal BP subjects with IFG in the Japanese population showed increased risks of CVD. To our knowledge, this study is the first on the combined impact of these borderline risk factors, IFG and prehypertension on the incidence of CVD in a general Asian population.

Previous cohort studies have shown that DM is a risk factor for CVD, stroke[14,15] and CHD.[13] The results of our study are also essentially compatible with the previous cohort studies in Japan. The Hisayama Study demonstrated that glucose intolerance for 2421 participants was a risk factor for increased incidence of stroke and CHD.[15] Iso *et al.*[20] reported that glucose abnormalities were a risk factor for ischemic stroke in a Japanese population by using nonfasting glucose levels. The NIPPON DATA 80 Study indicated that DM, defined by nonfasting blood glucose levels, was a risk factor for CVD mortality.[33] In the Funagata Diabetes Study, IFG was not a risk factor

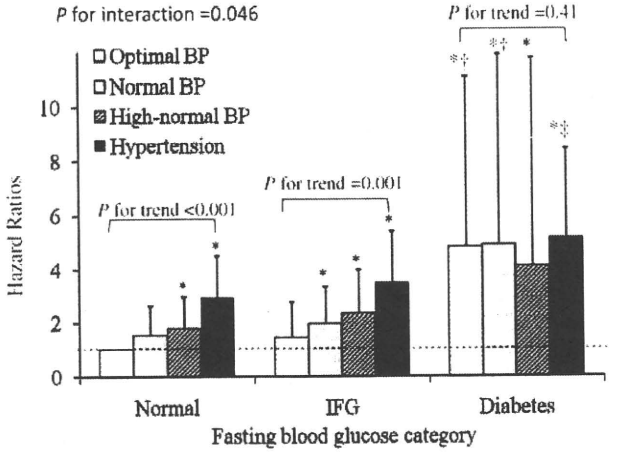

Figure 2 The influence of fasting glucose and BP categories on multivariable-adjusted hazard ratios and 95% confidence intervals for the incidence of cardiovascular disease. *$P<0.05$, compared with normoglycemic subjects with optimal BP. †$P<0.05$, compared with normoglycemic subjects in the same BP category. ‡$P<0.05$, compared with normoglycemic subjects with hypertension.

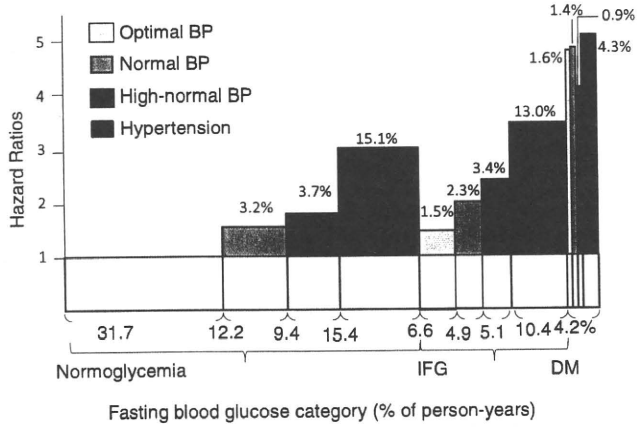

Figure 3 The hazard ratios and population attributable fractions for CVD to exposure to the combined impact of glucose (normoglycemia, impaired fasting glucose and diabetes) and blood pressure categories (optimal, normal, and high-normal blood pressures and hypertension) at baseline were estimated. The gray and black areas represent excessive incidence of CVD in the high blood glucose and high blood pressure categories compared with the subjects with normoglycemia and optimal blood pressure as a reference.

for CVD mortality, although impaired glucose tolerance was a risk factor for CVD.[34]

Compared with previous studies, our study has several methodological strengths. First, our cohort population was relatively large and was selected at random from an urban population in contrast to most other cohort populations in Asia, which were selected from rural populations.[15,20,34] Second, all of our cohort participants were examined at one place and measured using the same autoanalyzer at one laboratory. Finally, our study examined the risk of CVD incidence, not CVD mortality.

In our study, we used the definitions of IFG and CVD/CHD set forth by the 2003 American Diabetes Association recommendations. In the Framingham Heart Study, the 2003 IFG definition was predictive of CHD in women but not in men,[17] a finding which was similar to our results. However, fewer studies have examined the association of the 2003 IFG definitions for CHD and stroke. Kanaya *et al.*[35] showed that the 2003 defination for IFG was not associated with increased risk of CHD or stroke among postmenopausal women with coronary artery disease.Kim *et al.*[36] reported that one-third of the population has IFG according to the 2003 definition. However, many of these individuals do not have increased prevalence of CHD.

Hu *et al.*[19] reported that hypertension and DM increased stroke risk independently and that their combination additively increased stroke risk. In our study, the risks of CVD in the normoglycemic and IFG groups were linearly related to the BP category (*P*-value for trend <0.001). However, the risks of CVD in the DM group did not change with BP category (*P*-value for trend=0.4), which was compatible with a previous result for trends between glucose category and hypertension status.[20] Recently, the ACCORD BP Study has shown that targeting an SBP <120 mm Hg, as opposed to an SBP <140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events in patients with type 2 diabetes.[37] Although present studies suggest that decreasing BP may be an effective way to prevent CVD in normoglycemic or IFG subjects, further investigations are required to clarify the interaction between the BP categories of DM subjects at risk for CVD in other large cohorts.

The percentage of the PAF for CVD incidence in normoglycemic subjects with high-normal BP or IFG subjects with normal or high-normal BP (PAF=12.6%) was 1.5 times higher than that in the DM subjects in any BP category (PAF=8.2%). Also, the PAF suggested that 12.6% of CVD cases would be preventable if the borderline glucose and blood pressure levels were controlled to within normoglycemic and optimal BP ranges.

Our results showed that hyperglycemia conferred a slightly higher risk of CVD incidence in women than in men, although men had greater absolute event rates for CVD. Previous studies have shown that the impact of DM on the risk of CVD is significantly greater in women than in men.[13,17,38] Lee *et al.* reported that the HRs of coronary heart disease for DM were 2.6 for women and 1.9 for men. In the Framingham Heart Study, [17] IFG was associated with increased CHD risk only in women (HR=1.7; 95% CI, 1.0–3.0). The reason for these sex differences in the association between DM and CVD remains unclear.

Our study has several limitations. The primary limitation is the regression dilution bias; this study was based on a single day measurement of serum glucose and BP levels.[39] That is, the fasting serum glucose and BP levels might have been misclassified. Second, as we did not perform glucose tolerance tests, we may have missed subjects with impaired glucose tolerance. Finally, we did not examine the combined effect of BP categories and glucose abnormalities after stratification by CVD subtypes, such as stroke and CHD because of the small sample size.

In conclusion, DM is a risk factor for CVD, stroke, and CHD, whereas an IFG of 5.6 to 6.9 mmol l^{-1} is a risk factor for CVD and CHD in women. The risks of CVD in the normoglycemic and IFG groups were linearly related to the BP category. The high-normal BP subjects in any glucose categories and the normal BP subjects with IFG showed increased risks of CVD in this Japanese population. Further investigations of larger cohorts of DM subjects are needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Dr Yasushi Kotani, all members of the Suita City Health Center and the Suita Medical Association. We also thank all researchers and the staff of the Division of Preventive Cardiology for performing the medical examinations and study follow-up. We also thank Satsuki-Junyukai, the volunteers who administered the Suita Study. Source of Funding: This study was supported by a Grant-in-Aid from the Ministry of Health, Labor and Welfare of Japan (H20-SeiShu-013 and H19-SeiShu-017); a research grant for cardiovascular disease from the Ministry of Health, Labor and Welfare (19S-6, 21S-1); and the Mitsui Life Social Welfare Foundation.

1 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I; Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.

2 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.

3 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003; **289**: 2560–2572.

4 Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; **345**: 1291–1297.

5 Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita Study. *Hypertension* 2008; **52**: 652–659.

6 Kokubo Y, Kamide K. High-normal blood pressure and the risk of cardiovascular disease. *Circ J* 2009; **73**: 1381–1385.

7 Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley Jr TH, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke* 2006; **37**: 2493–2498.

8 Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, Noda H, Tanigawa T, Iso H, Shimamoto T. Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). *Stroke* 2009; **40**: 1571–1577.

9 Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Kiyohara Y. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. *Circulation* 2008; **118**: 2672–2678.

10 Fox CS, Coady S, Sorlie PD, D'Agostino Sr RB, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. *Circulation* 2007; **115**: 1544–1550.

11 Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes* 1974; **23**: 105–111.

12 Manuel DG, Schultz SE. Health-related quality of life and health-adjusted life expectancy of people with diabetes in Ontario, Canada, 1996–1997. *Diabetes Care* 2004; **27**: 407–414.

13 Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 2000; **23**: 962–968.

14 Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss G. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Diabetes Care* 1999; **22**: 1077–1083.

15 Doi Y, Ninomiya T, Hata J, Fukuhara M, Yonemoto K, Iwase M, Iida M, Kiyohara Y. Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population: the Hisayama Study. *Stroke* 2010; **41**: 203–209.

16 Wingard DL, Barrett-Connor EL, Scheidt-Nave C, McPhillips JB. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care* 1993; **16**: 1022–1025.

17 Levitzky YS, Pencina MJ, D'Agostino RB, Meigs JB, Murabito JM, Vasan RS, Fox CS. Impact of impaired fasting glucose on cardiovascular disease: the Framingham Heart Study. *J Am Coll Cardiol* 2008; **51**: 264–270.

18 Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; **26**: 3160–3167.

19 Hu G, Sarti C, Jousilahti P, Peltonen M, Qiao Q, Antikainen R, Tuomilehto J. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* 2005; **36**: 2538–2543.

20 Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, Ohira T, Yamagishi K, Iida M, Shimamoto T. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. *Diabetologia* 2004; **47**: 2137–2144.

21 Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care* 2005; **28**: 355–359.

22 Hu G, Jousilahti P, Tuomilehto J. Joint effects of history of hypertension at baseline and type 2 diabetes at baseline and during follow-up on the risk of coronary heart disease. *Eur Heart J* 2007; **28**: 3059–3066.

23 Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, Higashiyama A, Kamide K, Kawanishi K, Okayama A, Kawano Y. The relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke* 2009; **40**: 2674–2679.

24 Kokubo Y, Okamura T, Yoshimasa Y, Miyamoto Y, Kawanishi K, Kotani Y, Okayama A, Tomoike H. Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: the Suita Study. *Hypertens Res* 2008; **31**: 2027–2035.

25 Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita Study. *Atherosclerosis* 2009; **203**: 587–592.

26 Watanabe M, Kokubo Y, Higashiyama A, Ono Y, Okayama A, Okamura T. New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: the Suita Study. *Diabetes Res Clin Pract* 2010; **88**: e20–e23.

27 Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Ono Y, Miyamoto Y, Yoshimasa Y, Okayama A. Triglycerides and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort: the Suita Study. *Atherosclerosis* 2010; **209**: 290–294.

28 Higashiyama A, Okamura T, Ono Y, Watanabe M, Kokubo Y, Okayama A. Risk of smoking and metabolic syndrome for incidence of cardiovascular disease—comparison of relative contribution in urban Japanese population: the Suita Study. *Circ J* 2009; **73**: 2258–2263.

29 Furukawa Y, Kokubo Y, Okamura T, Watanabe M, Higashiyama A, Ono Y, Kawanishi K, Okayama A, Date C. The relationship between waist circumference and the risk of stroke and myocardial infarction in a Japanese urban cohort: the Suita Study. *Stroke* 2010; **41**: 550–553.

30 Walker AE, Robins M, Weinfeld FD. The national survey of stroke. Clinical findings. *Stroke* 1981; **12**: I13–I44.

31 Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**: 583–612.

32 Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88**: 15–19.

33 Kadowaki S, Okamura T, Hozawa A, Kadowaki T, Kadota A, Murakami Y, Nakamura K, Saitoh S, Nakamura Y, Hayakawa T, Kita Y, Okayama A, Ueshima H. Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. NIPPON DATA 80. *Diabetologia* 2008; **51**: 575–582.

34 Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 1999; **22**: 920–924.

35 Kanaya AM, Herrington D, Vittinghoff E, Lin F, Bittner V, Cauley JA, Hulley S, Barrett-Connor E. Impaired fasting glucose and cardiovascular outcomes in postmenopausal women with coronary artery disease. *Ann Intern Med* 2005; **142**: 813–820.

36 Kim SH, Chunawala L, Linde R, Reaven GM. Comparison of the 1997 and 2003 American Diabetes Association classification of impaired fasting glucose: impact on prevalence of impaired fasting glucose, coronary heart disease risk factors, and coronary heart disease in a community-based medical practice. *J Am Coll Cardiol* 2006; **48**: 293–297.

37 ACCORD Study Group. Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of Intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1575–1585.

38 Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; **265**: 627–631.

39 MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.

Lifetime Risk of Stroke in Japan

Tanvir Chowdhury Turin, MBBS; Yoshihiro Kokubo, MD; Yoshitaka Murakami, PhD; Aya Higashiyama, MD; Nahid Rumana, MBBS; Makoto Watanabe, MD; Tomonori Okamura, MD

Background and Purpose—Lifetime risk (LTR) is an epidemiologic measure that expresses the probability of disease in the remaining lifetime for an index age. The LTR for stroke has not been reported for the Japanese population.

Methods—We included all participants from the Suita Study who were cardiovascular disease–free at baseline. Age (in years) was used as the time scale. Age-specific stroke incidence and all-cause mortality were calculated with the person-year method, and we estimated the sex- and index age–specific LTRs of first-ever stroke and its subtypes, taking into account the competing risk of death.

Results—We followed up 5498 participants from 1989 to 2005 for a total of 67 475 person-years. At age 55 years, the LTR for stroke, after accounting for competing risks of death, was 18.3% for men and 19.6% for women. The LTR for cerebral infarction was 14.6% for men and 15.5% for women, and the LTR for intracerebral hemorrhage was 2.4% for men and 1.4% for women at the index age of 55 years. The LTR for stroke remained similar across other index ages of 45, 55, and 65 years.

Conclusions—The observed probabilities illustrate that ≈1 in 5 men and women of middle age will experience stroke in their remaining lifetime. This easy understandable information can be used as an important index to assist in public health education and planning. (***Stroke*. 2010;41:1552-1554.**)

Key Words: lifetime risk ■ stroke ■ Japan

Despite decades of declining mortality from stroke since the 1960s,[1,2] stroke remains the third most common cause of death in Japan.[3] With the aging of the population and an unfavorable cardiovascular risk factor scenario, stroke is likely to become an increasingly important health burden in Japan. Thus, prevention activities for stroke require urgent attention.

Estimation of the lifetime risk (LTR) of stroke, which provides an absolute risk assessment and would be more easily understood by the general population, can be useful in public health education. This index has the potential to promote early detection efforts, increase awareness, and motivate beneficial changes in lifestyle or health behaviors. The LTR of stroke has not yet been reported for the Japanese population. In the present study, we estimated the short- intermediate-term risk and LTR of stroke and its subtypes in Japanese.

Subjects and Methods

Study Sample

The Suita Study, a cohort study of cardiovascular disease established in 1989, randomly sampled Suita city residents, age 30 to 79 years, by sex and age class (10-year increments).[4] From this sample, 6485 participated in the baseline survey (participation rate, 53%) at the National Cardiovascular Center in Osaka. After we excluded participants with a past history of cardiovascular disease (n=208) and those who did not participate in the baseline survey or were lost to follow-up (n=779), data for the remaining 5498 participants (2571 men and 2927 women) were included in this analysis. Follow-up for the current study ended at the time of stroke occurrence, at death, or on December 31, 2005, whichever came first.

Identifying possible stroke events involved checking the health status of all participants by repeated clinical visits every 2 years and yearly questionnaires by mail or telephone. All hospitalizations and deaths during the previous year were identified. To complete our surveillance for fatal events, we conducted a systematic search of death certificates for Suita City residents by accessing the National Vital Statistics database, with the permission from the Management and Coordination Agency of Japan. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Diseases by the end of 1994 and the 10th International Classification of Diseases from the beginning of 1995. All data (health check-ups, questionnaires, telephone queries, and death certificates) were checked against medical records to confirm the incidence of stroke. In-hospital medical records of participants who were suspected of having had a stroke were reviewed by registered hospital physicians or research physicians, who were blinded to the baseline information. Using criteria adopted from the US National Survey of Stroke,[5] we defined a stroke event as a sudden or rapid onset of neurologic symptoms lasting for >24 hours or leading to death, in the absence of evidence of a nonstroke cause. Strokes were classified as cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage, based on computed tomography, magnetic resonance imaging, or autopsy findings. This study was approved by the institutional review board of the National Cardiovascular Center.

Received February 7, 2010; accepted March 12, 2010.

From the Department of Health Science (T.C.T., A.H., N.R.), Shiga University of Medical Science, Shiga; Department of Preventive Cardiology (T.C.T., Y.K., A.H., M.W., T.O.), National Cardiovascular Center, Osaka; and Department of Medical Statistics (Y.M.), Shiga University of Medical Science, Shiga, Japan.

Correspondence to Tanvir Chowdhury Turin, Department of Health Science, Shiga University of Medical Science, Otsu City, Shiga, 520-2192, Japan. E-mail dr.turin@gmail.com, turin@belle.shiga-med.ac.jp

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.581363**

Table. Age- and Sex- Specific 10-, 20-, 30-, and 40-Year and Lifetime Risk Estimates for Stroke and its Subtypes: Suita Study, 17-Year Follow-Up, 1989–2005, Japan

			Unaccounted for Competing Risk of Death					Accounted for Competing Risk of Death				
			Short- and Intermediate-Term Risks					Short- and Intermediate-Term Risks				
Stroke Type	Sex	Index Age, y	10-Year	20-Year	30-Year	40-Year	Lifetime Risk	10-Year	20-Year	30-Year	40-Year	Lifetime Risk
All stroke	Men	45	0.65	3.27	8.79	18.50	27.93	0.65	3.15	7.90	14.42	18.93
		55	2.62	8.13	17.84		27.27	2.50	7.26	13.77		18.28
		65	5.52	15.23			24.65	4.76	11.27			15.70
		75	9.71				19.14	6.51				11.02
	Women	45	0.62	2.09	4.62	13.01	24.67	0.61	2.05	4.43	11.55	20.18
		55	1.47	4.00	12.40		24.05	1.44	3.82	10.94		19.57
		65	2.53	10.92			22.58	2.38	9.50			18.13
		75	8.39				20.05	7.12				15.75
Cerebral infarction	Men	45	0.32	2.44	5.95	13.61	22.87	0.32	2.34	5.36	10.54	14.95
		55	2.12	5.63	13.29		22.55	2.03	5.04	10.22		14.63
		65	3.51	11.17			20.43	3.02	8.19			12.61
		75	7.66				16.92	5.18				9.59
	Women	45	0.12	0.65	1.91	8.04	19.65	0.12	0.63	1.81	7.01	15.60
		55	0.53	1.79	7.92		19.53	0.51	1.70	6.90		15.48
		65	1.26	7.39			19.00	1.18	6.38			14.97
		75	6.13				17.74	5.20				13.79
Cerebral hemorrhage	Men	45	0.00	0.38	1.78	3.43	3.05	0.00	0.36	1.58	2.42	2.42
		55	0.38	1.78	3.05		3.05	0.36	1.58	2.42		2.42
		65	1.40	2.67			2.67	1.22	2.05			2.05
		75	1.26				1.26	0.84				0.84
	Women	45	0.25	0.57	1.14	1.77	1.77	0.24	0.56	1.09	1.64	1.64
		55	0.32	0.89	1.53		1.53	0.31	0.85	1.39		1.39
		65	0.57	1.20			1.20	0.53	1.08			1.08
		75	0.64				0.64	0.54				0.54
Subarachnoid hemorrhage	Men	45	0.17	0.17	0.57	0.89	0.89	0.17	0.17	0.51	0.71	0.71
		55	0.00	0.40	0.72		0.72	0.00	0.34	0.54		0.54
		65	0.40	0.72			0.72	0.34	0.54			0.54
		75	0.31				0.31	0.20				0.20
	Women	45	0.25	0.78	1.43	2.07	2.93	0.25	0.77	1.38	1.93	2.58
		55	0.53	1.18	1.81		2.67	0.51	1.13	1.67		2.33
		65	0.65	1.29			2.14	0.62	1.16			1.81
		75	0.63				1.49	0.54				1.19

All risk values are expressed as percentages. To account for the competing risk of death on the probability of stroke; we estimated LTR conditional on survival to an index age, by executing a multiple-decrement procedure and taking into consideration both the occurrence of an event and death from any cause.

Statistical Analysis

The residual LTR has been defined in 2 ways in the literature[6]: (1) lifetime cumulative incidence that indicates the cumulative risk for the remaining lifetime but does not account for the impact of mortality due to competing causes and (2) lifetime cumulative incidence that accounts for competing risk of death. We estimated both statistics in our study.

The incidence rate of stroke and all-cause morality rate were estimated in 5-years age increments by the person-year method.[7] The probability of developing stroke was computed by applying these age-specific incidence and mortality rates. The number of individuals at risk for stroke at age $t+1$, N_{t+1}, and the number of incident cases at age $t+1$, n_{t+1}, were calculated with the following formulas:

$$N_{t+1}=N_t\times(1-m_t-r_t)$$

$$n_{t+1}=r_{t+1}\times N_{t+1}$$

where N_t is the number of individuals at risk at the index age t; m_t is all-cause mortality at age t; and r_t and r_{t+1} are the incidences of the event at ages t and $t+1$, respectively.

The numerator of LTR (expressed in percent) was the total number of incident cases that accumulated after the specified index age, and the denominator of LTR was the number of individuals at risk at the index age. LTR estimates were extended to 95 years of age because few participants survived past 94 years. The numerator of LTR for index age i was determined with the following formula:

$$\sum_{t=i}^{94} n_t$$

The LTR for index age i (with the population at risk at age i equal to N_i) was determined from the formula

$$LTR_i=\frac{\sum_{t=i}^{94} n_t}{N_i}$$

We estimated sex-specific 10-, 20-, 30-, and 40-year risks and the LTR at different index ages for stroke and its subtypes. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

Results

We had 67 475 person-years of observation. The incidence rate was 392.8 per 100 000 person-years for men and 253.6

per 100 000 person-years for women during the follow-up period.

The Table presents the 10-, 20-, 30-, and 40-year risks and LTR for all stroke and stroke subtypes in men and women who reached various index ages. Accounting for competing risks of death attenuated the estimates of the cumulative incidence for stroke to some extent for all index ages and for both sexes. There was a graded increase in stroke risk with increasing time span. For all strokes, the 10-year risk at age 45 was 0.7%, and this increased for the 20-, 30-, and 40-year risk categories to 3.2%, 7.9%, and 14.4%, respectively. This phenomenon was observed in both sexes and for all stroke subtypes. With regard to stroke subtype, the LTR of ischemic stroke was higher than that for hemorrhagic stroke. This was observed in both men and women and at all index ages.

Discussion

To the best of our knowledge, this is the first report to present the LTR of stroke in any non-Western population. The LTR of stroke in our study was similar to the reported LTR in the Framingham[8] or Rotterdam[9] study. The LTRs of stroke for middle-aged adults were substantial. The observed probabilities illustrate that ≈1 in 5 men and women of middle age will experience stroke. This risk was higher for cerebral infarction (for men, 1 in 7 and for women, 1 in 6) than for cerebral hemorrhage (for men, 1 in 40 and for women, 1 in 60) or subarachnoid hemorrhage (for men, 1 in 200 and for women, 1 in 50). The LTR was similar for the index ages of 45, 55, and 65 years.

The strengths of our study include the use of a population-based cohort and the fact that our estimates were based on simultaneously gathered data on both stroke incidence and other-cause mortality attributable to the competing risk of death in the same cohort. The incidence of stroke and its subtypes in our study population is similar to that in other population-based or cohort studies in Japan.[10,11] During recent decades in Japan, ischemic stroke has been reported to be the dominant subtype as a proportion of all strokes, being 3 to 4 times more frequent than cerebral hemorrhage,[10,11] which is similar to our findings.

Our LTR estimates are useful for public education because they are easier to comprehend than are measures such as incidence, prevalence, or relative risk.[12] LTR is a more generalizable approach to health education because it avoids the common problems associated with complicated numeracy or low quantitative literacy.[13] A recent study with focus group discussions has concluded that patients preferred health risks to be framed in absolute terms and a lifetime estimate on a scale of "x out of 100."[14] In particular, the interpretation with the reciprocal number of probability estimated in our study, for example, that 1 in 5 men of 45 years will have a stroke during their lifetime, presents the risk of stroke in an intuitively comprehensible form.

In Japan, it has been reported that the incidence of stroke has declined over time, but recent evidence suggests that the incidence might have leveled off during the last few decades.[15] With stroke incidence being stagnant and the LTR estimates presented herein that 1 in 5 of middle-age and older adults are likely to develop stroke during their remaining lifetime, our results emphasize that stroke poses a major threat as a public health burden. In younger individuals with low short-term risks, the high LTR might be more useful to motivate lifestyle modifications, with appropriate health education efforts aimed at prevention of stroke, thereby reducing the population burden of stroke.

Sources of Funding

The present study was supported by the Ministry of Health, Labor, and Welfare (H19-Seishu-017, H19-Seishu-021, H20-Seishu-013, and 21S-1). Tanvir Chowdhury Turin and Nahid Rumana are supported by fellowships and research grants-in-aid (P-20.08124 and P-21.09139) from the Japan Society for the Promotion of Science.

Disclosures

None.

References

1. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. *Stroke*. 2000;31:1588–1601.
2. Liu L, Ikeda Y, Yamori Y. Changes in stroke mortality rates for 1950 to 1997: a great slowdown of decline trend in Japan. *Stroke*. 2001;32:1745–1749.
3. Health and Welfare Statistics Association. *2003 Kokumin Eisei no Doko (Trend for National Health and Hygiene, Japan)*. Tokyo: Health and Welfare Statistics Association; 2003 (in Japanese).
4. Kokubo Y, Nakamura S, Okamura T, Yoshimasa Y, Makino H, Watanabe M, Higashiyama A, Kamide K, Kawanishi K, Okayama A, Kawano Y. Relationships between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke*. 2009;40:2674–2679.
5. Walker AE, Robins M, Weinfeld FD. The national survey of stroke: clinical findings. *Stroke*. 1981;12(pt 2, suppl 1):I-13–I-44.
6. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *J Am Med Assoc*. 2002;287:1003–1010.
7. Berslow NE, Day NE. *Statistical Methods in Cancer Research, Vol II: the Analysis of Case-Control Studies*. Lyon: International Agency for Research on Cancer; 1980:41–81.
8. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, Wolf PA. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006;37:345–350.
9. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM. Incidence, risk, and case fatality of first ever stroke in the elderly population: the Rotterdam Study. *J Neurol Neurosurg Psychiatry*. 2003;74:317–321.
10. Kita Y, Okayama A, Ueshima H, Wada M, Nozaki A, Choudhury SR, Bonita R, Inamoto Y, Kasamatsu T. Stroke incidence and case fatality in Shiga, Japan, 1989–1993. *Int J Epidemiol*. 1999;28:1059–1065.
11. Ishikawa S, Kayaba K, Gotoh T, Nago N, Nakamura Y, Tsutsumi A, Kajii E. Incidence of total stroke, stroke subtypes, and myocardial infarction in the Japanese population: the JMS Cohort Study. *J Epidemiol*. 2008;18:144–150.
12. Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. *BMJ*. 2002;324:827–830.
13. Schwartz LM, Woloshin S, Welch HG. Risk communication in clinical practice: putting cancer in context. *J Natl Cancer Inst Monogr*. 1999;25:124–133.
14. Fortin JM, Hirota LK, Bond BE, O'Connor AM, Col NF. Identifying patient preferences for communicating risk estimates: a descriptive pilot study. *BMC Med Inform Decis Mak*. 2001;1:2.
15. Kita Y, Turin TC, Ichikawa M, Sugihara H, Morita Y, Tomioka N, Rumana N, Okayama A, Nakamura Y, Abbott RD, Ueshima H. Trend of stroke incidence in a Japanese population: Takashima Stroke Registry, 1990–2001. *Int J Stroke*. 2009;4:241–249.

Nephrol Dial Transplant (2010) 1 of 8
doi: 10.1093/ndt/gfq062

NDT
Nephrology Dialysis Transplantation

Original Article

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 community 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:

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

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:

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

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).