on the foot, vibration perception was regarded as compromised. Autonomic function was evaluated by measuring the coefficient of variation of the R-R interval (CV_{R-R}) during deep breathing monitored on an electrocardiogram. The patients were also classified as current smokers or nonsmokers. Nonsmokers were defined as not having consumed tobacco for at least the previous 3 years.

An MRI scanner at 1.5-Tesla (Signa Horizon-LX; GE Medical Systems, Milwaukee, WI, USA) was used at entry and at endpoint of the study for the following experimental protocols as previously described [22]. Briefly, after at least 15 min of rest, all patients were evaluated in the supine position in a temperature-controlled room at 25 −C. To set up the individual flow analysis, the popliteal artery was depicted by 2D time-of-flight magnetic resonance angiography. A single slice with 5-mm thickness at the popliteal artery was oriented perpendicular to the flow direction, and flow data throughout the cardiac cycle were obtained using 2D-cine-PC MRI with 80-cm/s velocity encoding triggered by peripheral gating. Heart rate was monitored by peripheral gating. Flow data were analysed on an Advantage Windows version 3.1 workstation (GE Medical Systems; Milwaukee, WI, USA) to determine direction and velocity through the cardiac cycle. The instantaneous flow volumes at 16 equally spaced time points through the cardiac cycle were calculated from the individual velocity images by integrating the velocity across the area of the vessel. The resultant 16 flow volumes allowed assessment of flow variations during the cardiac cycle. Total flow volume was calculated from the integration of the waveform. A resistive index, which associates with peripheral vascular resistance to blood flow, has been defined as (A-B)/A, where A is the systolic peak velocity and B is the end-diastolic velocity. The resistive index was calculated from the 16 velocity images originally obtained.

Statistical evaluation was performed on SPSS software version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparison between the two groups was performed using the unpaired student's t-test. Paired t-test was used to compare two sets of paired observations. The chi-square test for two-by-two contingency tables was used to compare frequencies between the groups. Simple linear regression analyses were performed to clarify the associations among glycaemic control and vascular parameters. To investigate the clinical variables determining blood flow in lower-leg arteries, we performed stepwise multiple regression analysis of the relation between change per year in total flow volume and nine possible risk factors for atherosclerosis (age, gender, duration of diabetes, smoking habit at entry and mean values of HbA_{1c}, TC, HDL-C, sBP, and dBP during the study) and three vascular parameters (change per year in ABI, baPWV and resistive index), three parameters of diabetic microangiopathy (retinopathy, nephropathy and neuropathy at entry) and use of three medications (insulin, statins and RAS inhibitors at entry) in diabetic patients. The F value was set at 4.0 at each step. Values are expressed as means 7 SD. *P* values less than 0.05 were considered to be statistically significant.

Results

All subjects at baseline

Clinical characteristics and vascular parameters of all subjects at entry are summarized in Table 1. There were no significant differences between diabetic patients and nondiabetic subjects in prevalence of male gender, age, body mass index (BMI), TC, dBP, smoking status, or ABI. However, the diabetic patients had higher HbA_{1c} ($p < 0.0001$), sBP ($p = 0.0008$), and baPWV ($p < 0.0001$) and lower HDL-C ($p = 0.0336$) and CV_{R-R} ($p < 0.0001$) than those of the nondiabetic subjects. Arterial waveforms at baseline are shown in Figure 1. Nondiabetic subjects (Figure 1A) showed a typically triphasic waveform, which was clearly separated into systolic, early diastolic, and late diastolic phases during the cardiac cycle. However, the diabetic patients (Figure 1B) showed a lower late diastolic flow component than that in the nondiabetic subjects. Quantitative blood flow measurements showed no significant differences in heart rate, systolic forward flow, and early diastolic flow reversal between the groups. However, compared with those in nondiabetic subjects, diabetic patients had a higher resistive index ($p < 0.0001$) and lower total ($p = 0.0044$) and late diastolic ($p < 0.0001$) flow volumes.

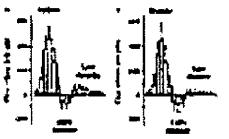

Figure 1. Arterial waveforms at the popliteal artery in nondiabetic subjects (A) and diabetic patients with normal ankle-brachial index (B) at baseline are shown. Instantaneous flow volumes at 16 equally spaced time points through the cardiac cycle are reconstructed. Data are means 7 SD [Normal View 11K | Magnified View 29K]

Table 1. Clinical characteristics and vascular parameters in all subjects at baseline

Group Number	Nondiabetic subjects 38	Diabetic patients 45	*p*-value
Male gender (%)	19 (50.0)	22 (48.9)	>0.9999
Age (years)	59.4 7 6.4	59.7 7 6.5	0.8658
BMI (kg/m^2)	22.7 7 1.7	23.0 7 4.6	0.7439
Duration of diabetes (years)	-	14.3 7 8.9	-
Treatment (diet/OHD/insulin)	-	1/16/28	-
			<0.0001

HbA_{1c} (%)	4.7 7 0.5	8.2 7 1.0	
TC (mmol/L)	4.92 7 0.58	4.84 7 0.87	0.6192
HDL-C (mmol/L)	1.44 7 0.43	1.26 7 0.35	0.0336
Statins (%)	-	18 (40.0)	-
Blood pressure (mmHg)			
Systolic	122 7 7	132 7 17	0.0008
Diastolic	76 7 7	72 7 10	0.1008
ACEI or ARB (%)	-	22 (48.9)	-
Smokers (%)	15 (39.5)	17 (37.8)	>0.9999
Retinopathy (%)	-	23 (51.1)	-
Micro- and macroalbuminuria (%)	-	18 (40.0)	-
Neuropathy (%)	-	20 (44.4)	-
CV_{R-R} (%)	3.31 7 1.07	2.28 7 1.02	<0.0001
ABI	1.12 7 0.09	1.13 7 0.07	0.4280
baPWV (cm/s)	1297 7 112	1691 7 317	<0.0001
Heart rate (bpm)	71 7 9	70 7 10	0.7639
Flow volume (mL/min)			
Total	90.2 7 17.9	77.2 7 22.0	0.0044
Systolic	84.5 7 16.8	82.6 7 18.0	0.6171
Early diastolic	-10.9 7 7.6	-13.1 7 10.6	0.2876
Late diastolic	16.7 7 6.5	7.7 7 8.3	<0.0001
Resistive index	0.971 7 0.024	1.013 7 0.039	<0.0001

Data are expressed as *n* (%) or means 7 SD. OHD, oral hypoglycaemic drug.

Risk factors

To clarify the risk factors for impaired peripheral circulation in lower-leg arteries in diabetic patients, clinical characteristics and vascular parameters at entry and at endpoint were compared, as shown in Table 2. At endpoint, 25 of the 45 (56%) diabetic patients showed decreased blood flow, and the remaining diabetic patients showed increased blood flow compared to baseline, resulting in similar blood flow at entry and endpoint. There were no significant differences in patients taking insulin, TC, HDL-C, statins, sBP, dBP, ACEI or ARB, prevalence of smokers, retinopathy, micro- and macroalbuminuria, or neuropathy, CV_{R-R}, ABI, heart rate or resistive index between entry and endpoint. However, at endpoint, BMI ($p = 0.0108$) and baPWV ($p = 0.0464$) were higher and HbA_{1c} ($p = 0.0057$) was lower than at baseline. To investigate the clinical variables determining blood flow in the lower-leg arteries, we performed stepwise multiple regression analysis of the relation between change per year in total flow volume and nine possible risk factors for atherosclerosis (age, gender, duration of diabetes, smoking habit at entry and mean values of HbA_{1c}, TC, HDL-C, sBP, and dBP during the study) and three vascular parameters (change per year in ABI, baPWV and resistive index), three parameters of diabetic microangiopathy (retinopathy, nephropathy and neuropathy at entry) and three medications (insulin, statins and RAS inhibitors at entry) in diabetic patients. Duration of diabetes at entry (β value = -0.183; F value = 4.281), mean values of HbA_{1c} during the study (β value = -6.083; F value = 22.072), use of RAS inhibitors at entry (β value = 4.602; F value = 8.413) and change per year in resistive index (β value = -348.777; F value = 29.944) were identified as significant independent variables determining change per year in blood flow ($r^2 = 0.733$, $p < 0.0001$) in diabetic patients.

Table 2. Clinical characteristics and vascular parameters in diabetic patients at entry and at endpoint

	At entry	At endpoint	*p*-value
BMI (kg/m^2)	23.0 7 4.6	24.2 7 3.2	0.0108
Treatment (diet/OHD/insulin)	1/16/28	0/10/35	0.2057
HbA_{1c} (%)	8.2 7 0.9	7.6 7 0.9	0.0057
TC (mmol/L)	4.84 7 0.86	4.98 7 0.70	0.2352
HDL-C (mmol/L)	1.26 7 0.36	1.27 7 0.33	0.6994
Statins (%)	18 (40.0)	21 (46.7)	0.6705
Blood pressure (mmHg)			

Systolic	132 7 17	135 7 16	0.3822
Diastolic	73 7 10	71 7 11	0.4469
ACEI or ARB (%)	22 (48.9)	23 (51.1)	>0.9999
Smokers (%)	17 (37.8)	14 (31.1)	0.6573
Retinopathy (%)	23 (51.1)	29 (64.4)	0.2859
Micro- and macroalbuminuria (%)	18 (40.0)	25 (55.6)	0.2055
Neuropathy (%)	20 (44.4)	23 (51.1)	0.6730
CV_{R-R} (%)	2.28 7 1.01	2.42 7 1.14	0.3459
ABI	1.13 7 0.07	1.15 7 0.09	0.1179
baPWV (cm/s)	1691 7 314	1758 7 315	0.0464
Heart rate (bpm)	70 7 10	72 7 11	0.4600
Flow volume (mL/min)			
Total	77.2 7 21.7	82.1 7 29.5	0.3221
Systolic	82.6 7 17.8	88.3 7 25.3	0.1510
Early diastolic	-13.1 7 10.4	-12.9 7 9.6	0.9085
Late diastolic	7.7 7 8.2	6.7 7 8.7	0.4551
Resistive index	1.013 7 0.039	1.013 7 0.045	0.9857

Data are expressed as *n* (%) or means 7 SD. OHD, oral hypoglycaemic drugs.

Peripheral circulation

To clarify the associations among vascular parameters, simple linear regression analyses were performed as shown in Figure 2. Change per year in total flow volume was negatively correlated with those in both baPWV ($p < 0.00001$) (Figure 2A) and resistive index ($p < 0.0001$) (Figure 2B). Furthermore, changes per year in baPWV and resistive index were positively correlated with each other ($p = 0.0004$) (Figure 2C). To clarify the associations of glycaemic control with vascular parameters, simple linear regression analyses were performed as shown in Figures 3 and 4. Change from baseline to endpoint in HbA_{1c} level was positively correlated with those in baPWV ($p = 0.0067$) (Figure 3A) and resistive index ($p = 0.0013$) (Figure 3B) and negatively with that in total flow volume ($p = 0.0008$) (Figure 3C). Mean HbA_{1c} during the study was positively correlated with changes per year in both baPWV ($p = 0.0022$) (Figure 4A) and resistive index ($p = 0.0014$) (Figure 4B) and negatively with that in total flow volume ($p < 0.0001$) (Figure 4C). The point where the line crosses the x-axis of mean HbA_{1c} during the study was 7.2% for baPWV, 7.3% for resistive index, and 7.8% for total flow volume, respectively.

Figure 2. Simple linear regression analyses among changes per year in total flow volume, brachial-ankle pulse wave velocity(baPWV) and resistive index in diabetic patients with normal ankle-brachial index. A: total flow volume *versus* baPWV; B: total flow volume *versus* resistive index; C: baPWV *versus* resistive index
[Normal View 14K | Magnified View 43K]

Figure 3. Simple linear regression analyses between change from baseline to endpoint in HbA_{1c} and brachial-ankle pulse wave velocity (baPWV) (A), resistive index (B) and total flow volume (C) in diabetic patients with normal ankle-brachial index
[Normal View 15K | Magnified View 43K]

Figure 4. Simple linear regression analyses of the association of mean HbA_{1c} during the study and changes per year in brachial-ankle pulse wave velocity (baPWV) (A), resistive index (B) and total flow volume (C) among diabetic patients with normal ankle-brachial index
[Normal View 14K | Magnified View 39K]

Discussion

Consistent with our previous report [4], diabetic patients with normal ABI have higher arterial stiffness, greater peripheral vascular resistance, and lower total and late diastolic flow volumes in lower-leg arteries than those in nondiabetic subjects. Blood flow is negatively correlated with arterial stiffness and peripheral vascular resistance in diabetic patients. These results suggest that higher arterial stiffness and greater peripheral vascular resistance contribute to the insufficient blood flow in lower-leg arteries in diabetic patients even without PAOD. Measurement of transcutaneous oxygen tension at dorsal

foot reflects blood flow in lower extremities, and is used to assess limb ischaemia in diabetic patients. As we reported previously [22], when the diagnostic criterion for critical limb ischaemia in diabetic patients with transcutaneous oxygen tension of <50 mmHg at dorsal foot is used [23], 27% of diabetic patients have ischaemic limb even though they have no PAOD. There are important differences between elastic and muscular arteries, but arterial distensibility is impaired in both types in diabetic patients [24][25]. Endothelial dysfunction [5], gradual accumulation of advanced glycation end products in the vessel wall [6], increased intima-media thickness [7][8], and vascular calcification [9][10] are responsible for the development of arterial rigidity in diabetic patients. Large arteries including the aorta and its major branches are characterized by the elastic properties of the vessel wall, and act as blood supply reservoirs as well as carrying vessels [26]. When arterial elasticity is decreased, less blood can be stored in these arteries, resulting in a decrease in late diastolic flow volume. Concomitantly, the medium- and small-caliber arteries and arterioles, which have vascular smooth muscles in the vessel wall, act as resistance vessels regulating blood flow to the capillaries [26]. Biopsy specimen from subcutaneous fat reveals that diabetic patients have greater peripheral vascular resistance due to endothelial dysfunction [11] or structural alteration [12] in small resistance arteries.

In this study at endpoint, 56% of diabetic patients showed decreased blood flow, and the remaining diabetic patients showed increased blood flow compared to baseline, resulting in similar blood flows at entry and at endpoint. Stepwise multiple regression analysis revealed that duration of diabetes, glycaemic control, use of ACEI or ARB and peripheral vascular resistance are independent variables determining blood flow in the lower-leg arteries in diabetic patients. Higher arterial stiffness, greater peripheral vascular resistance, and lower blood flow in lower-leg arteries were associated with mean values of HbA_{1c} during the study in diabetic patients. These results indicate that long-term exposure to hyperglycaemia impairs blood flow in lower-leg arteries in diabetic patients without PAOD. The points where the lines cross the x-axis of mean HbA_{1c} during the study for arterial stiffness, peripheral vascular resistance, and blood flow in lower-leg arteries ranged from 7.2% to 7.8%, and these values are higher than the recommended glycaemic goal for HbA_{1c} level less than 7.0% [20]. Use of statins, ACEI or ARB ameliorates endothelial function in diabetic patients [16-18], while some studies suggest no effect of treatment with statins on endothelial function in diabetic patients [27][28]. Insulin stimulates synthesis of endothelial vasodilators and improves arterial function by decreasing large artery stiffness and increasing vasodilation of small resistance arteries [29], but these effects are attenuated in diabetic patients [30]. These results suggest that administration of ACEI or ARB might protect blood flow in lower-leg arteries against long-term hyperglycaemia and contribute to higher HbA_{1c} than the recommended glycaemic goal.

Among the limitations of this study, our treatment goals were higher than the recommended target goal of HbA_{1c} level less than 7.0%. Thus, administration of ACEI or ARB may have beneficial effects to protect blood flow in lower-leg arteries against long-term hyperglycaemia in diabetic patients. In addition, our blood sampling data include both overnight fasting and postprandial following occasional episodes of hypoglycaemia.

In conclusion, although our study is a retrospective study design, we have demonstrated for the first time that higher arterial stiffness, greater peripheral vascular resistance and lower blood flow in lower-leg arteries are associated with long-term hyperglycaemia in type 2 diabetic patients even without PAOD. Benefits of improved glycaemic control on blood flow in lower-leg arteries were observed at HbA_{1c} level less than 7.0%. Thus, our data support a recommended glycaemic goal for HbA_{1c} level less than 7.0%, with additional treatment suggested for individuals with HbA_{1c} level greater than 8.0%.

Conflict of interest

None declared.

REFERENCES

1 Faglia E, Favales F, Quarantiello A, *et al.* Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. *Diabetes Care* 1998; **21**: 625-630. Links

2 American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003; **26**: 3333-3341. Links

3 Orchard TJ, Strandness DE Jr. Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Heart Association and the American Diabetes Association 18-20 September 1992, New Orleans, Louisiana. *Diabetes Care* 1993; **16**: 1199-1209. Links

4 Suzuki E, Kashiwagi A, Nishio Y, *et al.* Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients. *Diabetes Care* 2001; **24**: 2107-2114. Links

5 Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1996; **27**: 567-574. Links

6 Airaksinen KE, Salmela PI, Linnaluoto MK, Ikäheimo MJ, Ahola K, Ryhänen LJ. Diminished arterial elasticity in diabetes: association with fluorescent advanced glycosylation end products in collagen. *Cardiovasc Res* 1993; **27**: 942-945. Links

7 Taniwaki H, Kawagishi T, Emoto M, *et al.* Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. *Diabetes Care* 1999; **22**: 1851-1857. Links

8 Yamasaki Y, Kodama M, Nishizawa H, *et al.* Carotid intima-media thickness in Japanese type 2 diabetic subjects:

predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* 2000; 23: 1310-1315. Links

9 Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia* 1993; 36: 615-621. Links

10 Lehto S, Niskanen L, Suhonen M, Rönnemaa T, Laakso M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol* 1996; 16: 978-983. Links

11 Rizzoni D, Porteri E, Guelfi D, *et al.* Endothelial dysfunction in small resistance arteries of patients with non-insulin-dependent diabetes mellitus. *J Hypertens* 2001; 19: 913-919. Links

12 Rizzoni D, Porteri E, Guelfi D, *et al.* Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus. *Circulation* 2001; 103: 1238-1244. Links

13 Nathan DM, Lachin J, Cleary P, *et al.* Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003; 348: 2294-2303. Links

14 Jensen-Urstad KJ, Reichard PG, Rosfors JS, Lindblad LE, Jensen-Urstad MT. Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. *Diabetes* 1996; 45: 1253-1258. Links

15 Rutherford RB, Baker JD, Ernst C, *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; 26: 517-538. Links

16 Tan KC, Chow WS, Tam SC, Ai VH, Lam CH, Lam KS. Atorvastatin lowers C-reactive protein and improves endothelium-dependent vasodilation in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2002; 87: 563-568. Links

17 O'Driscoll G, Green D, Maiorana A, Stanton K, Colreavy F, Taylor R. Improvement in endothelial function by angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1999; 33: 1506-1511. Links

18 Cheetham C, Collis J, O'Driscoll G, Stanton K, Taylor R, Green D. Losartan, an angiotensin type 1 receptor antagonist, improves endothelial function in non-insulin-dependent diabetes. *J Am Coll Cardiol* 2000; 36: 1461-1466. Links

19 Yamashina A, Tomiyama H, Takeda K, *et al.* Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; 25: 359-364. Links

20 American Diabetes Association. Standards of medical care in diabetes - 2008. *Diabetes Care* 2008; 31: S12-S54. Links

21 Boulton AJ, Vinik AI, Arezzo JC, *et al.* Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; 28: 956-962. Links

22 Suzuki E, Kashiwagi A, Nishio Y, *et al.* Usefulness of waveform analysis of popliteal artery in type II diabetic patients using gated magnetic resonance 2D-cine-PC imaging and ^{31}P spectroscopy. *Diabetologia* 2000; 43: 1031-1038. Links

23 Faglia E, Mantero M, Caminiti M, *et al.* Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. *J Intern Med* 2002; 252: 225-232. Links

24 Giannattasio C, Failla M, Grappiolo A, Gamba PL, Paleari F, Mancia G. Progression of large artery structural and functional alterations in type 1 diabetes. *Diabetologia* 2001; 44: 203-208. Links

25 Henry RM, Kostense PJ, Spijkerman AM, *et al.* Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. *Circulation* 2003; 107: 2089-2095. Links

26 London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J* 1999; 138: 220-224. Links

27 Economides PA, Caselli A, Tiani E, Khaodhiar L, Horton ES, Veves A. The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes. *J Clin Endocrinol Metab* 2004; 89: 740-747. Links

28 van de Ree MA, Huisman MV, de Man FH, van der Vijver JC, Meinders AE, Blauw GJ. Impaired endothelium-dependent vasodilation in type 2 diabetes mellitus and the lack of effect of simvastatin. *Cardiovasc Res* 2001; 52: 299-305. Links

29 Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. *J Clin Invest* 1994; 94: 2511-2515. Links

30 Tamminen M, Westerbacka J, Vehkavaara S, Yki-Järvinen H. Insulin-induced decreases in aortic wave reflection and central systolic pressure are impaired in Type 2 diabetes. *Diabetes Care* 2002; 25: 2314-2319. Links

Diabetes Metab. Res. Rev. Vol.9999, 9999 Pages: n/a

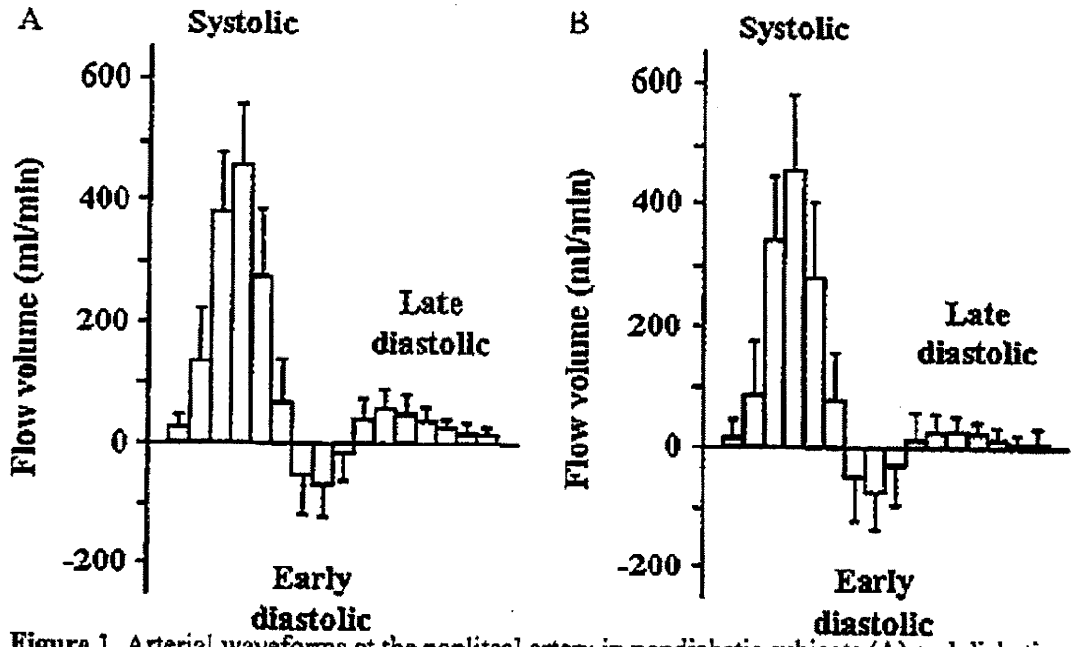

Figure 1. Arterial waveforms at the popliteal artery in nondiabetic subjects (A) and diabetic patients with normal ankle-brachial index (B) at baseline are shown. Instantaneous flow volumes at 16 equally spaced time points through the cardiac cycle are reconstructed. Data are means 7 SD

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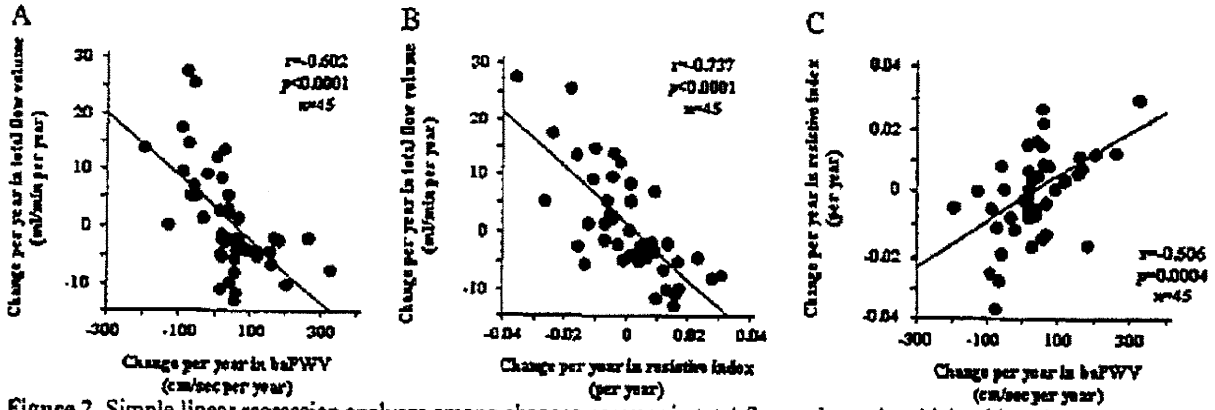

Figure 2. Simple linear regression analyses among changes per year in total flow volume, brachial-ankle pulse wave velocity(baPWV) and resistive index in diabetic patients with normal ankle-brachial index. A: total flow volume *versus* baPWV; B: total flow volume *versus* resistive index; C: baPWV *versus* resistive index

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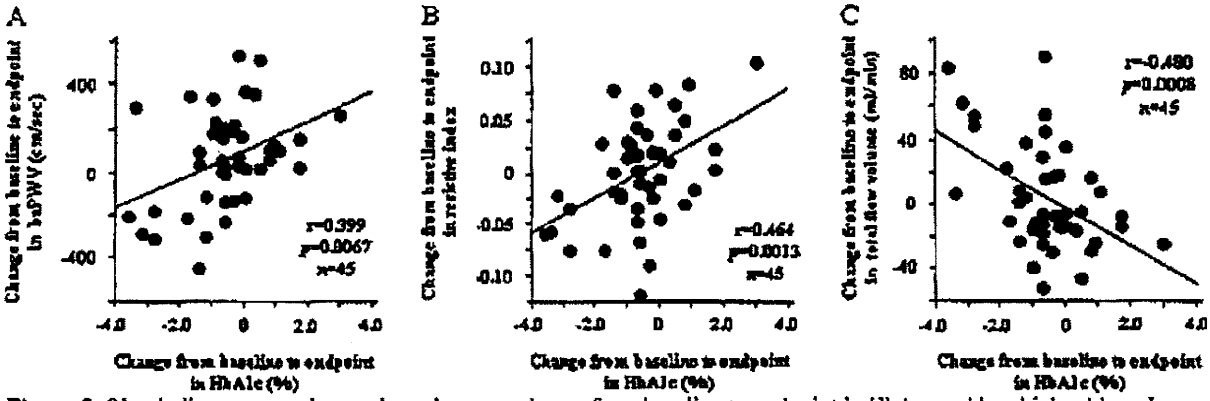

Figure 3. Simple linear regression analyses between change from baseline to endpoint in HbA_{1c} and brachial-ankle pulse wave velocity (baPWV) (A), resistive index (B) and total flow volume (C) in diabetic patients with normal ankle-brachial index

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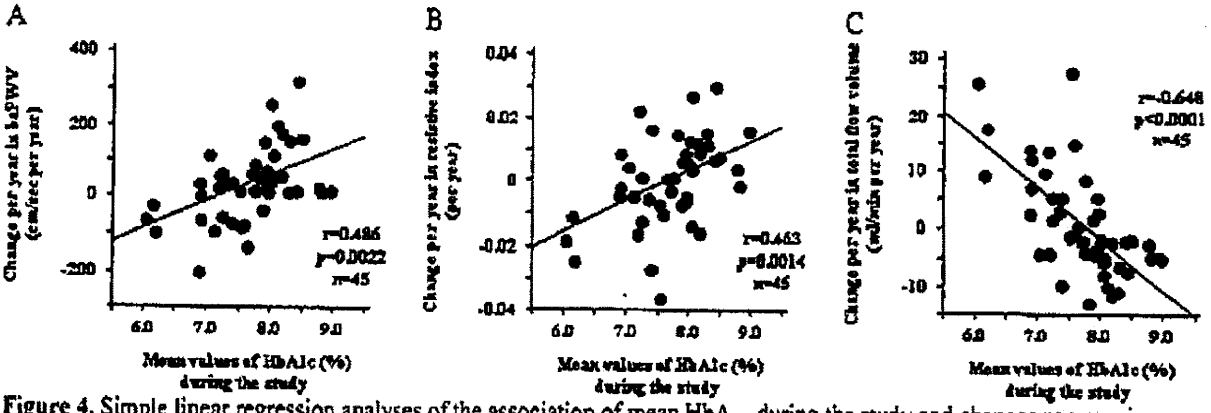

Figure 4. Simple linear regression analyses of the association of mean HbA_{1c} during the study and changes per year in brachial-ankle pulse wave velocity (baPWV) (A), resistive index (B) and total flow volume (C) among diabetic patients with normal ankle-brachial index

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Original Article

Self-reported Diabetes Mellitus and Risk of Mortality from All Causes, Cardiovascular Disease, and Cancer in Takayama: A Population-based Prospective Cohort Study in Japan

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ABSTRACT

Background: Diabetes mellitus has been reported to be a major risk factor for cardiovascular disease (CVD), and higher risk of CVD among women than that among men has been observed in many studies. Further, the association of diabetes with increasing risk of cancer has also been reported. Well-designed studies conducted among men and women in the general Japanese population remain scarce.

Methods: Our cohort consisted of 13355 men and 15724 women residing in Takayama, Japan, in 1992. At the baseline, the subjects reported diabetes in a questionnaire. Any deaths occurring in the cohort until 1999 were noted by using data from the Office of the National Vital Statistics. The risk of mortality was separately assessed for men and women by using a Cox proportional hazard model after adjusting for age; smoking status; body mass index (BMI); physical activity; years of education; history of hypertension; and intake of total energy, vegetables, fat, and alcohol.

Results: Diabetes significantly increased the risk of mortality from all causes [hazard ratio (HR): 1.35, 95% confidence interval (CI): 1.11-1.64] and from coronary heart disease (CHD) (HR: 2.96, 95% CI: 1.59-5.50) among men, and that from all causes (HR: 1.74, 95% CI: 1.34-2.26) and cancer (HR: 1.88, 95% CI: 1.16-3.05) among women. Diabetes was not significantly associated with mortality from CHD among women.

Conclusion: The findings suggest that diabetes increases the risk of mortality from CVD among men and that from cancer among women. The absence of increased risk of mortality from CHD among women may suggest a particular pattern in the Japanese population.

Key words: Diabetes mellitus, Mortality, Cardiovascular disease, Cancer, Cohort study

INTRODUCTION

Diabetes mellitus is a major risk factor of cardiovascular disease (CVD), and epidemiological studies from different areas have reported that people with diabetes are at higher risk of mortality from CVD and from all causes.[1-4] Japan was ranked fifth among the World Health Organization member states in terms of the estimated number of cases of diabetes, and the increased risk of mortality among people with diabetes imposes a significant health burden on the nation. A previous study reported that the relative effect of diabetes on the risks of mortality from CVD and all causes among the Asian population did not differ from those among the Caucasian population.[5] The same study also reported that the CVD risks associated with diabetes were similar in men and women. However, detailed information regarding each cohort from Japan that contributed to the study has not yet been published and was therefore unavailable. Another study in Japan indicated that the increase in the risk of heart disease among diabetic patients was slightly higher in men than in women, although the study was not based on an underlying observational epidemiological study, and comparison was made between the data of diabetic patients and population statistics.[6] One prospective study in Japan reported that the presence of diabetes increased the risk of CVD, and another study conducted on atomic bomb survivors reported an

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association between HbA1c and mortality from CVD.[7,8] In both these studies, the combined risks for men and women were calculated, and the number of participants included was rather limited. Another study has reported an increase in the risk of CVD in diabetic patients,[9] although the participants of this study were not selected from the general population but consisted of patients. Thus, a study on a large cohort of men and women selected from the general Japanese population in order to assess the relationship between diabetes and the risk of mortality from CVD and all causes is desired.

It has also been reported that diabetes is associated with an increased risk of cancer. Moreover, studies conducted in Japan and those conducted abroad have reported a relationship of the risk of cancer or specific cancer in several sites with diabetes and with the HbA1c and fasting plasma glucose levels.[8,10-14] Cancer is the leading cause of death in Japan, and mortality from cancer exceeds that from CVD in both men and women.[15,16] The risk of cancer mortality in diabetic patients is likely to have an impact on the nation's public health.

The aim of the current study is to conduct a prospective cohort study to assess the association between diabetes and mortality from CVD, cancer, and all causes. We examined the male-female difference in the risks of mortality associated with diabetes. Our cohort was community-based and was selected from the general Japanese population, and the risks were assessed after considering the risk factors for CVD and cancer.

METHODS

Study Participants

The data were obtained from the Takayama study in Japan. The details of the Takayama study have been described elsewhere.[17-19] In brief, the study population consisted of men and women who were residents of Takayama City and were 35 years or older in 1992. At the baseline, a self-administered questionnaire was administered to 36990 residents, and a 92.0% response rate was obtained. Of the participants who responded to the questionnaire, those who did not complete more than 45% of it (n = 595, 1.7%) and those who gave unreliable or inconsistent responses (n = 1871, 5.5%) were excluded from the cohort. The final fixed cohort consisted of 31552 subjects, including 14427 men and 17125 women. Physician diagnoses of diabetes and other major diseases, including hypertension, were reported in the questionnaire in response to the question "Have you ever been told by a physician that you have following diseases?" The participants answered this question for each listed disease. Those who reported a history of cancer, myocardial infarction, angina, or stroke were excluded from the cohort. The final cohort for the current study consisted of 29079 subjects, including 13355 men and 15724 women.

Information regarding the baseline characteristics of the study cohort, such as age; height; weight; cigarette smoking; use of medication, including aspirin; and length of education in years, was reported in the questionnaire. Women's health issues, including menopausal status and use of hormone replacement therapy, were also asked in the questionnaire. In addition, a semi-quantitative, validated, food-frequency questionnaire (FFQ) that quantified 169 food items was administered.[17] From the FFQ data, the total daily calorie intake and the intake of each nutrient and food item were estimated according to the Japanese Standard Tables of Food Composition, 5th edition, published by the Science and Technology Agency of Japan. Detailed information on the FFQ, including its validity and reproducibility, has been previously described.[17] The amount of regular physical activity was estimated from the validated questionnaire and expressed in terms of metabolic equivalents per week.[20,21]

Ascertainment of Mortality

Deaths in the cohort that occurred between September 1992 and December 1999 were recorded. After obtaining permission from the Ministry of Internal Affairs and Communication to review the data regarding deaths, each cause of death was confirmed using the data from the Office of the National Vital Statistics. The major endpoint of this study was mortality from all causes, CVD, cancer, and causes other than cancer and CVD. We further analyzed mortality from several diseases that were frequently observed in the cohort. The Statistics and Information Department of the Japanese Ministry of Health and Welfare listed all the causes of deaths, which were coded according to the International Classification of Diseases, 10th Revision (ICD-10). Deaths from cancer were classified as codes C00 through C97, and deaths from CVD, as codes I00 through I99 and Q25 through Q28.

Data Analysis

The age-adjusted mortality rates per 10000 person-years classified according to the status of diabetes were separately calculated for men and women by standardization to the rate among subjects of the Takayama study by sex and by 10-year age category. We compared the characteristics of the participants with and without diabetes by using *t* tests for continuous variables and chi-square tests for categorical variables. The intake of each food and nutrient was logarithmically transformed for statistical testing in order to approximately normalize its distribution. To assess the magnitude of the association of diabetes with mortality from each cause, a Cox proportional hazard model was applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). To track the subjects who moved out of the study area we referred to the city residential registers, and these subjects were counted as censored subjects. Age was included in the model for adjustment since it is a potent risk factor for

diabetes, CVD, and cancer. We also considered a multivariate model with adjustments for other factors that were associated with diabetes: age; smoking status; body mass index (BMI); physical activity; years of education; history of hypertension; total energy intake; and intake of vegetables, fat, and alcohol. The intake of each food and nutrient in the model was adjusted for the total energy intake by using the regression analysis proposed by Willett.[22] All statistical analyses were performed using SAS (SAS Institute Inc., Gary, NC).

RESULTS

At the baseline, 5.9% males and 2.7% females reported that they had diabetes. Table 1 summarizes the baseline characteristics of the participants by the diabetes status in both men and women. The subjects with diabetes were significantly older, and their BMI was slightly but significantly higher than that of non-diabetic subjects. The subjects with diabetes were less physically active, more frequently reported a history of hypertension, and their caloric intake was significantly lower than the subjects without diabetes.

During the follow up, 1163 deaths occurred in men over 91036.7 person-years, and 899 deaths occurred in women over 110123.1 person-years. Standardized mortality rates by the diabetes status and the HRs of mortality among men are shown in Table 2. The risks of mortality from all causes and from coronary heart disease (CHD) were significantly higher among diabetic men than among non-diabetic men. Further analysis of the disease-specific mortality by using multivariate adjustment showed an increased risk of mortality from liver cancer (HR: 4.30, 95% CI: 1.98-9.38) among diabetic men as compared with that among non-diabetic men.

The standardized mortality rates by the status of diabetes and the HRs of mortality among women are shown in Table 3. The risks of mortality from all causes, cancer, and causes other than cancer and CVD were significantly higher among diabetic women than among non-diabetic women. The risks of mortality from CHD and stroke, and the total CVD risk did not differ between diabetic and non-diabetic women. Further analysis of the mortality from several diseases by using multivariate adjustment revealed a higher risk of mortality from colorectal cancer (HR: 4.30, 95% CI: 1.78-10.41) among diabetic women than among non-diabetic women. We repeated the analysis after excluding women who reported the current use of hormone replacement therapy, and the results were essentially the same.

DISCUSSION

The current study suggests that self-reported diabetes

Table 1. Baseline characteristics of 13355 men and 15724 women by diabetes status in Takayama, Japan, 1992-1999

	Men					Women				
	Without Diabetes n = 12561		With Diabetes n = 794		Two-sided *P* value†	Without Diabetes n = 15301		With Diabetes n = 423		Two-sided *P* value†
	Mean (± standard deviation)					Mean (± standard deviation)				
Age (y)	53.7	(12.1)	58.5	(11.0)	<0.01	54.9	(13.0)	63.1	(11.8)	<0.01
Body mass index (kg/m^2)	22.5	(2.8)	23.0	(2.8)	<0.01	22.0	(2.9)	22.4	(3.3)	<0.01
Height (cm)	164.8	(6.8)	163.7	(6.8)	<0.01	152.1	(6.4)	150.1	(6.1)	<0.01
Physical activity (MET/week)	27.3	(41.7)	23.4	(38.3)	0.01	18.9	(29.8)	14.4	(23.1)	<0.01
Total energy intake (kcal/d)	2610	(868)	2504	(872)	<0.01	2115	(778)	1877	(708)	<0.01
Total vegetable intake (g/d)	370.0	(258.6)	408.1	(287.3)	<0.01	393.4	(264.2)	431.9	(288.7)	0.01
Total fat intake (g/d)	61.2	(28.6)	60.7	(27.8)	0.64	55.5	(26.6)	49.3	(25.0)	<0.01
Total alcohol intake (g/d)	42.1	(41.4)	39.5	(43.2)	<0.01	7.8	(16.9)	4.3	(11.8)	<0.01
	No. (%)					No. (%)				
Currently married	11380	(90.6)	713	(89.8)	0.46	11380	(74.4)	251	(59.3)	<0.01
Education 12 years or more	5358	(42.7)	299	(37.7)	0.01	5151	(33.7)	85	(20.1)	<0.01
Cigarette smoking status*										
Never smoker	2051	(16.3)	127	(16.0)	<0.01	11328	(74.0)	296	(70.0)	0.04
Current smoker	6757	(53.8)	375	(47.2)		1800	(11.8)	52	(12.3)	
Former smoker	3394	(27.0)	265	(33.4)		600	(3.9)	14	(3.3)	
History of hypertension	2279	(18.1)	246	(31.0)	<0.01	2605	(17.0)	124	(29.3)	<0.01
Aspirin use within the past 6 months	508	(4.0)	39	(4.9)	0.23	1,043	(6.8)	19	(4.5)	0.06
Post-menopausal women						8680	(56.7)	351	(83.0)	<0.01
Current hormone replacement therapy use						239	(1.6)	10	(2.4)	0.19

* Do not add up to 100% because of missing data
† *t* test for continuous variables and chi-square test for categorical variables

Table 2. Age-adjusted mortality from cardiovascular disease, cancers, and all causes of death and the hazard ratios (HRs) of the mortalities among diabetic and non-diabetic men in the Takayama study

Cause of death	ICD-10 Code	Men without diabetes		Men with diabetes		Age-adjusted	95% CI		Multivariate†	95% CI	
		Death (n)	Mortality rate per 10000 person-year*	Death (n)	Mortality rate per 10000 person-year*	HR			HR		
All deaths		1050	124.83	113	165.32	1.26	1.04	1.53	1.35	1.11	1.64
Cancer	C00-C97	363	43.24	37	53.62	1.21	0.87	1.70	1.33	0.94	1.87
Cardiovascular disease	I00-I99	267	31.73	41	60.20	1.79	1.29	2.49	1.82	1.30	2.53
Coronary heart disease	I20-I25	45	5.36	13	18.37	3.05	1.66	5.61	2.96	1.59	5.50
Stroke	I60-I64, I67, I69, Q25-Q28	120	14.27	17	23.91	1.64	0.99	2.73	1.65	0.99	2.76
Deaths not from cancer or cardiovascular disease		420	49.86	35	51.50	0.97	0.69	1.37	1.05	0.74	1.49

* Age standardized to that of the male participants of the Takayama study
† Adjusted for age; smoking status; BMI; physical activity; length of education in years; history of hypertension; total energy intake; and intake of vegetables, fat, and alcohol
ICD-10: International Classification of Diseases, 10th revision, CI: confidence interval

Table 3. Age-adjusted mortality from cardiovascular disease, cancers, and all causes of death and the hazard ratios (HRs) of the mortalities among diabetic and non-diabetic women in the Takayama study

Cause of death	ICD-10 Code	Women without diabetes		Women with diabetes		Age-adjusted	95% CI		Multivariate†	95% CI	
		Death (n)	Mortality rate per 10000 person-year*	Death (n)	Mortality rate per 10000 person-year*	HR			HR		
All deaths		836	79.26	63	137.65	1.71	1.32	2.21	1.74	1.34	2.26
Cancer	C00-C97	235	22.19	18	38.58	1.92	1.19	3.10	1.88	1.16	3.05
Cardiovascular disease	I00-I99	309	29.36	18	35.59	1.31	0.81	2.10	1.36	0.84	2.20
Coronary heart disease	I20-I25	46	4.37	2	3.85	0.91	0.22	3.73	0.49	0.07	3.57
Stroke	I60-I64, I67, I69, Q25-Q28	127	12.06	5	10.34	0.88	0.36	2.15	0.88	0.36	2.16
Deaths not from cancer or cardiovascular disease		292	27.70	27	63.48	2.09	1.41	3.10	2.09	1.39	3.14

* Age standardized to that of the female participants of the Takayama study
† Adjusted for age; smoking status; BMI; physical activity; length of education in years; history of hypertension; total energy intake; and intake of vegetables, fat and alcohol
ICD-10: International Classification of Diseases, 10th revision, CI: confidence interval

increases the risk of mortality from all causes in men and women, from CVD in men, and from cancer in women. The results partially contradict those of previous studies conducted mainly in Western countries, which repeatedly reported that diabetic women have a higher risk of CVD and that they lose their advantages over men regarding CVD.[4,23-30] It was reported in a review of previously conducted epidemiological studies that the age-adjusted mortality rates for CHD were 2 to 3 times higher among diabetic men and 3 to 7 times higher among diabetic women in population-based studies.[29] However, since 1996, 4 meta-analyses were conducted on the topic of the higher risk of CHD among women than among men, and the results were rather contradictory: Three studies concluded that compared with men, women with diabetes were at increased risk of mortality from CHD, and 1 study found no difference between men and women.[3,4,31,32]

A previous study in Japan compared data from patients with diabetes and population statistics and showed that the risk of heart disease among diabetic women did not exceed that among diabetic men. The ratio of the observed number of deaths from heart disease among diabetic patients to the number expected on the basis of population statistics was 1.93 ($P < 0.01$) in men and 1.58 (not significant) in women.[6] A study that assessed the association between random blood glucose levels and the risk of ischemic stroke also did not show a distinct difference in the risk between diabetic men and women; the relative risk was 1.8 (95% CI 1.0-3.2) for men and 2.2 (95% CI 1.2-4.0) for women.[33] These 2 studies were not included in the above meta-analyses; they might not meet the inclusion criteria because of their study design or because the participants were not selected from the general population. Other prospective cohort studies in Japan did not assess the relationship between diabetes and the risk of mortality for men and women separately; instead, sex was adjusted in the model, presumably because of the limited number of participants or because the studies were not originally concerned about the sex differences in the magnitude of risk.[7-9]

The previously reported higher risk of CVD among women with diabetes relative to that among men with diabetes might be due to obesity, since obesity has been observed to be more prevalent among diabetic women than diabetic men in several studies conducted in the US.[30,34,35] In our cohort, the mean BMI among women with diabetes (22.0 kg/m^2) was nearly equal to the mean BMI among women without diabetes (22.4 kg/m^2), but the difference between the two was nevertheless statistically significant. We considered the possibility that women with lower BMIs were more likely to report diabetes. Consistent with the findings of the current study, the findings of previous studies showed that the BMIs of people with diabetes were similar to those of the general population in Japan.[36] The average BMI was 23.1 kg/m^2 among male and female participants with diabetes in the Japan Diabetes Complications Study,[37] while the average BMI among a similar age group in the general Japanese population ranged between 22.90-23.70 kg/m^2.[38] The smoking status may also have influenced the association between diabetes and mortality from CVD among women since it had been previously reported that cigarette smoking increased the risk of CVD mortality among women with diabetes.[39] However, only about 15% of women were current or former smokers in our study. Our stratified analysis by smoking status failed to show any differences of the risks between the stratum with regard to the mortality from CVD among diabetic women compared to that among non-diabetic women (data not shown). Nonetheless, we cannot eliminate the possibility that as compared to men, women in the current study had less severe diabetes, and that this was responsible for the smaller risk of CVD observed among women. Information on the severity of diabetes was unavailable in the current study.

In the current study, diabetic women had increased risk of mortality from cancer. This may be partly attributable to the increased risk of colon and colorectal cancer observed among diabetic women. In contrast, an association between diabetes and mortality from cancer was not found among men. The results of a previous prospective cohort study that assessed the risk of mortality from colon/colorectal cancer were inconsistent in terms of variation by sex.[11,40,41]

The risk of mortality from causes other than CVD and cancer was higher among diabetic women than among non-diabetic women. Of the causes of mortality other than cancer and CVD, diabetes was the most frequently observed among diabetic women. A total of 12 diabetic women died as a result of diabetes (ICD-10 codes: E10-E14), and the age-standardized mortality rate from all causes other than cancer and CVD was 27.27 per 10000 person-years, which was relatively higher than the equivalent rate among diabetic men, 14.06 per 10000 person-years. Further detailed information on mortality was not available; however, mortality as a result of diabetes may be caused by acute complications, and we speculate that this might have overtaken the mortality from CVD.

The current study has several advantages. The study was conducted in a community-based cohort selected from the general Japanese population, and the participation rate was relatively high. Mortality within the cohort was prospectively followed up, and deaths from all causes were confirmed using the data from the Ministry. Potential multiple confounders of the association between the status of diabetes and mortality were adjusted for the analysis.

Nevertheless, the current study has several limitations. The diagnosis of diabetes was reported in a questionnaire, and the validity and reliability of the report was undetermined. Fortunately, the positive predictive value for self-reported diabetes among Japanese subjects in a previous study was high (82%), and substantial agreement was found between the diabetic patients identified using questionnaires and those

identified using confirmed medical records.[42] Nevertheless, it is possible that a certain proportion of men and women who had diabetes did not report it in the current study. A study conducted by the Japanese Ministry of Health, Labour and Welfare estimated that the prevalence of diabetes among Japanese people who were 50 years or older was more than 14.2% in men and more than 7.1% in women in 1997. These values are considerably higher than those estimated at the baseline of the current study for both men and women, although in the study by the Health Ministry, the estimations were made using the hemoglobin A1c test, and this study was conducted 5 years after the initiation of the current study.[43] Such underreporting could introduce bias in the estimation of the association between diabetes and mortality. Despite the limitations of self-reported diabetes, as in the current study, several previous large-scale epidemiological studies among the general population used self-reported diabetes to assess its association with the risk of cancer or other conditions.[12,42] Further, some other studies assessed this association and did not use the oral glucose test or medical record review to validate self-reported diabetes.[11,44-46] Such misclassification, caused by the underestimation of the true prevalence of diabetes, would bias the analysis of the association toward the null when true association exists, and thereby attenuate the association. Furthermore, information on diabetes was only available at the baseline, and diabetes that may have developed during the follow-up period was not considered. Data on hyperlipidemia, a traditional risk factor of CVD, were not available in our study. In a recent report from the Asia Pacific Cohort Studies Collaboration,[47] the mean total cholesterol level was 5.34 mmol/L in people with diabetes and 5.11 mmol/L in people without diabetes, and these levels are relatively similar. The risk of CHD increased both for persons with diabetes and for persons without diabetes; an approximately 2-fold increase was observed when the highest fourth of the total cholesterol (approximately 6.3 mmol/L) was compared to the lowest fourth (approximately 4.5 mmol/L).[47] Considering the 3-fold increase in the risk of mortality from CHD in men with diabetes observed in the current study, the positive association would not be negated even after taking the effect of total cholesterol into account. Moreover, the size of the cohort may not have been sufficiently large to assess the risk of mortality, especially considering the mortality from some diseases with relatively low mortality rates.

Despite the limitations, the current study provides valuable information regarding the risk of mortality among diabetic men and women. For both men and women, an increased risk of mortality from all causes was suggested. Among men with self-reported diabetes, an increased risk of death from CVD was observed, and among women with self-reported diabetes, an increased risk of death from cancer was observed. The observed variation in the risk by sex was not fully explained in the current study, but with further investigation, a distinct pattern of the risk of mortality among people with diabetes in the Japanese population may emerge.

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REFERENCES

1. Meigs JB. Epidemiology of cardiovascular complications in type 2 diabetes mellitus. Acta Diabetol 2003;40:S358-61.
2. Marks JB, Raskin P. Cardiovascular risk in diabetes: a brief review. J Diabetes Complications 2000;14:108-15.
3. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. Arch Intern Med 2002;162:1737-45.
4. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73-8.
5. Woodward M, Zhang X, Barzi F, Pan W, Ueshima H, Rodgers A, et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. Diabetes Care 2003;26:360-6.
6. Sasaki A, Horiuchi N, Hasegawa K, Uehara M. Mortality and causes of death in type 2 diabetic patients. A long-term follow-up study in Osaka District, Japan. Diabetes Res Clin Pract 1989;7:33-40.
7. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, et al. Diabetes and cardiovascular disease in a prospective population survey in Japan: The Hisayama Study. Diabetes 1996;45:S14-6.
8. Nakanishi S, Yamada M, Hattori N, Suzuki G. Relationship between HbA(1)c and mortality in a Japanese population. Diabetologia. 2005;48:230-4.
9. Shimamoto K, Kita T, Mabuchi H, Matsuzaki M, Matsuzawa Y, Nakaya N, et al. Effects of hypertension and type 2 diabetes mellitus on the risk of total cardiovascular events in Japanese patients with hypercholesterolemia: implications from the Japan Lipid Intervention Trial (J-LIT). Hypertens Res 2007;30:119-23.
10. Czyzyk A, Szczepanik Z. Diabetes mellitus and cancer. Eur J Intern Med 2000;11:245-2.
11. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004;159:1160-7.
12. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871-7.
13. Qiu D, Kurosawa M, Lin Y, Inaba Y, Matsuba T, Kikuchi S, et al. Overview of the epidemiology of pancreatic cancer focusing on the JACC Study. J Epidemiol 2005;15:S157-67.
14. Yamagata H, Kiyohara Y, Nakamura S, Kubo M, Tanizaki Y,

Matsumoto T, et al. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. Diabetes Care 2005;28:789-94.
15. Health and Welfare Statistics Association. Kokumin-eisei-no-doko (Annual statistical report of national health conditions). Health and Welfare Statistics Association: Tokyo; 2007 (in Japanese).
16. Health and Welfare Statistics Association. Statistical abstracts on health and welfare in Japan 2006. Tokyo (Japan): Health and Welfare Statistics Association; 2006.
17. Shimizu H, Ohwaki A, Kurisu Y, Takatsuka N, Ido M, Kawakami N, et al. Validity and reproducibility of a quantitative food frequency questionnaire for a cohort study in Japan. Jpn J Clin Oncol 1999;29:38-44.
18. Shimizu H. The basic report on Takayama Study. Gifu: Department of Public Health, Gifu University School of Medicine; 1996.
19. Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, et al. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. Cancer Lett 2006;244:260-7.
20. Suzuki I, Kawakami N, Shimizu H. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. J Epidemiol 1998;8:152-9.
21. Shimizu H. A supplementary comment on "Reliability and validity of a questionnaire for assessment of physical activity in epidemiological studies" published in Journal of Epidemiology, 1998. J Epidemiol 2002;12:54.
22. Willett WC. Implications of total energy intake for epidemiologic analyses. In: Willett WC, editor. Nutritional epidemiology. New York: Oxford University Press 1990;245-71.
23. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035-8.
24. Gorodeski GI. Impact of the menopause on the epidemiology and risk factors of coronary artery heart disease in women. Exp Gerontol 1994;29:357-75.
25. Lundberg V, Stegmayr B, Asplund K, Eliasson M, Huhtasaari F. Diabetes as a risk factor for myocardial infarction: population and gender perspectives. J Intern Med 1997;241:485-92.
26. Resnick HE, Howard BV. Diabetes and cardiovascular disease. Annu Rev Med 2002;53:245-67.
27. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. Stroke 1996;27:63-8.
28. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 1994;43:960-7.
29. Manson JE, Tosteson H, Ridker PM, Satterfield S, Hebert P, O'Connor GT, et al. The primary prevention of myocardial infarction. N Engl J Med 1992;326:1406-16.
30. Imazu M, Sumii K, Yamamoto H, Toyofuku M, Tadehara F, Okubo M, et al. Influence of type 2 diabetes mellitus on cardiovascular disease mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Diabetes Res Clin Pract 2002;57:61-9.
31. Orchard TJ. The impact of gender and general risk factors on the occurrence of atherosclerotic vascular disease in non-insulin-dependent diabetes mellitus. Ann Med 1996;28:323-33.
32. 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;23:962-8.
33. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia 2004;47:2137-44.
34. Resnick HE, Valsania P, Halter JB, Lin X. Differential effects of BMI on diabetes risk among black and white Americans. Diabetes Care 1998;21:1828-35.
35. Harris MI. Epidemiological correlates of NIDDM in Hispanics, whites, and blacks in the U.S. population. Diabetes Care 1991;14:639-48.
36. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. Lancet 2003;361:85.
37. Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, et al. Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three year-interim report. Horm Metab Res 2002;34:509-15.
38. Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990-1994. Int J Obes Relat Metab Disord 1998;22:684-7.
39. Al-Delaimy WK, Willett WC, Manson JE, Speizer FE, Hu FB. Smoking and mortality among women with type 2 diabetes: The Nurses' Health Study cohort. Diabetes Care 2001;24:2043-8.
40. Limburg PJ, Anderson KE, Johnson TW, Jacobs DR Jr, Lazovich D, Hong CP, et al. Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2005;14:133-7.
41. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194-202.
42. Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A, et al. Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabet Med 2005;22:323-31.
43. Japanese Ministry of Health, Labour and Welfare. Available from: http://www.mhlw.go.jp/shingi/2004/03/s0318-15.html (in Japanese).
44. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control 1998;9:403-10.
45. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev 2007;16:276-80.
46. Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med 2001;161:242-7.
47. Asia Pacific Cohort Studies Collaboration. Cholesterol, diabetes and major cardiovascular diseases in the Asia-Pacific region. Diabetologia 2007;50:2289-97.

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Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women

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Abstract

We assessed the relationship of the dietary glycemic index (GI), glycemic load (GL), and intake of carbohydrate and rice, and risk of mortality from stroke and its subtypes. The cohort consisted of 12 561 men and 15 301 women residing in Takayama, Japan, in 1992. At the baseline, a food frequency questionnaire was administered; and the dietary GI, GL, and intake of carbohydrates and rice were estimated. Deaths from stroke occurring in the cohort were prospectively noted until 1999 with data from the office of the National Vital Statistics. The risk of mortality from stroke was assessed with a Cox proportional hazard model after adjusting for age; body mass index; smoking status; physical activity; history of hypertension; education; and intake of total energy, alcohol, dietary fiber, salt, and total fat. The risk of stroke subtypes was assessed in the age-adjusted model. The hazard ratios of total stroke comparing the highest vs the lowest quartiles of the dietary GI were 0.78 (95% confidence interval [CI], 0.41-1.47) with P_{trend} = .50 in men and 2.09 (95% CI, 1.01-4.31) with P_{trend} = .10 in women. Among women, the association was also significant with the risk of ischemic stroke (hazard ratio = 2.45; 95% CI, 1.01-5.92; P_{trend} = .03); and a significant positive trend was also observed between dietary GL and mortality from hemorrhagic stroke (P_{trend} = .05). The current study implies that diets with a high dietary GI increase the risk of mortality from stroke among Japanese women.

1. Introduction

Stroke is a common condition in Japan, and risk of death due to stroke was about twice of that in the United States and other Western countries from 1950 through 1987 [1]. Mortality from stroke has been declining in following years, but it is still the third leading cause of death in Japan [2]. Prospective epidemiologic studies have provided little information concerning the relationship among the dietary glycemic index (GI), glycemic load (GL), and risk of stroke. A few studies have evaluated the association and suggested that the dietary GL increases the risk of stroke [3-5]. These studies were conducted in Western countries, and no report has yet been published concerning Asian populations. Carbohydrate consumption is high in Japan; and its major source is white rice, which is high in dietary GI. Research into the potential health effects of GI, GL, carbohydrates, and rice is of particular interest in this population.

We therefore conducted a prospective study among Japanese men and women in a community-based cohort to obtain information on the relationship of the dietary GI, GL, intake of carbohydrates and rice, and the risk of stroke. It might be beneficial to study the specific types of stroke because each subtype of stroke has its own risk factors [6,7]. We also assessed the risk of subtypes of stroke in the current study.

2. Materials and methods

2.1. Study participants

The data were provided by the Takayama study in Japan. The details of the Takayama study have been described

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elsewhere [8-10]. Briefly, the study population was men and women residing in Takayama City who were 35 years or older in 1992. At the baseline, a self-administered questionnaire was conducted to the 36 990 residents to collect information on the baseline characteristics of the study cohort such as age, height, weight, and length of education. Physician diagnoses of major diseases including hypertension, cancer, myocardial infarction or angina, stroke, and diabetes were also reported in the questionnaire. Of the participants who responded to the questionnaire, those who did not complete more than 45% of it and those who gave unreliable or inconsistent responses were excluded. Based on the answers to the food frequency questionnaire (FFQ) administered at the same time, subjects who answered only 16 items or fewer, who were regarded to be responded by the other person, who selected the food frequency category of "Never" for all food items, or who selected the food frequency category of "Once a day" or "Two or more times a day" for continuous 40 food items or over were excluded from the study [9]. In addition, subjects who reported to have staple food (any kind of rice, bread, flour, or noodles) 5 times or more, meat 7 times or more, fish 7 times or more, or ethanol 400 mL or more per day were excluded [9].

The final fixed cohort consisted of 31 552 subjects, 14 427 men and 17 125 women, yielding a response rate of 85.3%. From them, the subjects who had cancer, myocardial infarction, angina, or diabetes were excluded from the cohort. Among men, 146 subjects had cancer; 787 subjects had myocardial infarction or angina; 794 subjects had diabetes; 15 subjects had cancer and either myocardial infarction or angina; 18 subjects had cancer and diabetes; 99 subjects had diabetes and either myocardial infarction or stroke; and 7 subjects had cancer, diabetes, and either myocardial infarction or angina. Among women, 476 subjects had cancer; 797 subjects had myocardial infarction or angina; 423 subjects had diabetes; 32 subjects had cancer and either myocardial infarction or angina; 27 subjects had cancer and diabetes; 64 subjects had diabetes and either myocardial infarction or stroke; and 5 subjects had cancer, diabetes, and either myocardial infarction or angina. After the exclusion, the final cohort for the current study consists of 27 862 subjects, 12 561 men and 15 301 women.

2.2. Estimation of nutrient intake, GI, and GL

The FFQ was previously validated and in a semiquantitative format measuring 169 food items [8]. From the FFQ, the total daily calorie intake and intake of each nutrient and food item, including carbohydrates, were estimated according to the *Japanese Standard Tables of Food Composition, Fifth Edition*, published by the Science and Technology Agency of Japan. Fatty-acid food composition was defined based on the data published by Sasaki et al [11]. The amount of rice intake was estimated from the FFQ in grams. Detailed information on the FFQ, including its validity and reproducibility, was previously described [8]. Updated Spearman correlation coefficients for men between the FFQ and 12-day food record were 0.34 for carbohydrate and 0.63 for dietary fiber. For women, they were 0.45 for carbohydrate and 0.60 for dietary fiber. We assigned GI values based on the international table of GI [12] and published data from studies in Japan [13,14]. Whenever there was more than one value, preference was given to data from Japanese studies. The carbohydrate intake after subtracting the dietary fiber intake was used for calculating the GI and GL values [13,14]. We used glucose as the reference. The foods for which only the white rice–based GI was available were transformed into glucose-based GI values by multiplying the white rice–based GI by 0.82 (=100/122) [14,15]. Of the 169 FFQ items, 8 items containing 3.5 g or more carbohydrates per serving had no GI values from the previous data. Because the carbohydrate content of these foods is still low and it is not likely that they will induce a significant rise in blood glucose, we assigned a 0 value to each one of them. The dietary GL was computed by summing the product of the carbohydrate intake from each food by the GI for that food and divided by 100. The dietary GI of each subject was obtained by dividing the dietary GL by the daily intake of total carbohydrate intake and multiplying by 100. The amount of regular physical activity was estimated from the validated questionnaire by ascertaining the average number of hours spent weekly performing various kinds of activities in the past year, and the information was calculated to determine the weekly metabolic equivalent [16].

2.3. Ascertainment of mortality

Deaths in the cohort were recorded between September 1992 and December 1999. In Japan, the underlying cause of death in the death certificates has been determined based on the rules defined by the World Health Organization [17]. After obtaining permission to review the death data from the Ministry of Internal Affairs and Communication, the cause of each death and the date were confirmed with data from the office of the National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare recorded the cause of death in each case, which was coded according to the International Classification of Diseases (ICD). The major end point of this study was mortality from stroke (ICD-9 codes 430-438 and ICD-10 codes I60-I69) and its subtypes: ischemic stroke (ICD-9 codes 434 and ICD-10 codes I63 and I69.3) and hemorrhagic stroke (ICD-9 codes 430 and 431 and ICD-10 codes I60, I61, I69.0, and I69.1). This study was approved by the Ethics Committee at Gifu University Graduate School of Medicine.

2.4. Data analysis

To assess the magnitude of the association of the dietary GI, GL, and intake of carbohydrates and rice to mortality from stroke, a Cox proportional hazard model was applied to estimate the hazard ratios (HRs) with 95% confidence

Table 1
Baseline characteristics by quartiles of dietary GI in 12 561 men and 15 301 women in the Takayama study, Japan, 1992

Variable[a]	Men					Women				
	Quartiles of dietary GI				Total	Quartiles of dietary GI				Total
	1	2	3	4		1	2	3	4	
	Mean (SD) or %					Mean (SD) or %				
Age (y)	54.4 (12.2)	53.9 (12.2)	53.3 (11.9)	53.0 (12.3)	53.7 (12.1)	54.3 (11.8)	54.4 (12.8)	54.9 (13.2)	56.1 (13.9)	54.9 (13.0)
BMI (kg/m^2)	22.5 (2.8)	22.6 (2.8)	22.4 (2.7)	22.5 (2.7)	22.5 (2.8)	22.0 (2.8)	22.0 (3.0)	22.0 (2.9)	21.8 (2.9)	22.0 (2.9)
Height (cm)	165.0 (6.6)	164.9 (6.9)	164.6 (6.8)	164.5 (7.0)	164.8 (6.8)	152.5 (6.1)	152.4 (6.3)	152.2 (6.3)	151.4 (6.7)	152.1 (6.4)
Exercise, metabolic equivalent (h/wk)	27.5 (42.1)	27.9 (42.4)	26.4 (39.8)	27.4 (42.5)	27.3 (41.7)	19.5 (29.6)	19.7 (30.9)	19.0 (30.1)	17.5 (28.4)	18.9 (29.8)
Current cigarette smokers (%)	57.8	56.7	55.7	51.3	55.4	15.5	13.0	12.1	11.9	13.1
Currently married (%)	91.9	92.0	92.4	89.8	91.5	75.9	76.4	76.5	73.7	75.6
Education ≥12 y (%)	43.5	43.4	43.5	42.5	43.2	37.5	36.5	34.3	28.6	34.2
Aspirin use within 6 mo (%)	4.7	4.1	4.1	3.3	4.0	7.7	7.1	6.6	5.9	6.8
Use of antihypertensive drug within 6 mo (%)	11.2	10.6	11.0	9.6	10.6	11.7	11.2	12.1	12.2	11.8
Current hormone replacement therapy in postmenopausal women (%)						2.7	2.4	1.5	1.6	2.0
Daily food and dietary intake										
GI	58.0 (3.1)	63.3 (1.0)	66.4 (0.9)	70.3 (2.0)	64.5 (4.9)	58.3 (2.9)	63.1 (0.9)	66.1 (0.9)	70.0 (2.0)	64.4 (4.7)
GL	202.8 (79.2)	228.0 (72.7)	233.7 (65.0)	237.2 (61.4)	225.4 (71.2)	183.4 (67.8)	184.7 (65.3)	193.9 (67.3)	201.9 (62.8)	191.0 (66.3)
Carbohydrate (g)	370 (144)	377 (120)	367 (102)	350 (91)	366 (116)	337 (127)	310 (109)	309 (107)	301 (94)	314 (111)
White rice (serving)[b]	2.3 (1.2)	3.2 (1.2)	3.7 (1.1)	4.0 (1.1)	3.3 (1.3)	1.9 (0.9)	2.3 (0.9)	2.7 (1.1)	3.2 (1.2)	2.6 (1.1)
Total energy (kcal)	2902 (1065)	2751 (872)	2537 (725)	2278 (640)	2617 (873)	2435 (907)	2148 (761)	2055 (720)	1884 (616)	2131 (784)
Alcohol (g)	58.5 (47.6)	45.9 (41.5)	36.6 (35.9)	27.6 (32.3)	42.1 (41.4)	10.9 (22.4)	8.5 (17.2)	6.9 (14.1)	5.1 (11.3)	7.8 (16.9)
Salt (g)	17.7 (7.7)	15.4 (6.0)	13.1 (4.8)	10.5 (4.1)	6.4 (1.5)	16.7 (6.9)	13.7 (5.4)	12.2 (4.7)	9.7 (3.9)	13.1 (5.9)
Polyunsaturated fat (g)	19.1 (8.9)	17.5 (7.3)	15.3 (6.1)	12.6 (5.2)	7.4 (2.4)	18.3 (8.0)	15.6 (6.7)	14.2 (6.1)	11.6 (5.0)	14.9 (7.0)
Monounsaturated fat (g)	25.1 (12.3)	22.5 (10.2)	19.4 (8.4)	15.8 (7.4)	10.3 (1.6)	23.6 (10.7)	19.7 (9.1)	17.6 (8.1)	14.0 (6.8)	18.7 (9.5)
Saturated fat (g)	20.8 (10.8)	17.9 (7.9)	15.3 (6.3)	12.3 (5.4)	8.5 (1.5)	20.4 (10.0)	16.1 (7.1)	14.1 (6.2)	11.1 (5.1)	15.4 (8.1)
Cholesterol (mg)	504 (251)	441 (203)	379 (176)	301 (153)	213 (19)	456 (220)	373 (173)	330 (155)	260 (138)	354 (188)
Protein (g)	110.0 (46.2)	99.6 (36.6)	88.5 (30.0)	74.9 (25.7)	37.8 (18.1)	100.9 (39.9)	84.6 (31.7)	77.2 (28.8)	65.4 (24.3)	82.0 (34.2)
Dietary fiber (g)	20.2 (11.6)	17.4 (8.2)	14.8 (6.3)	12.1 (5.0)	8.7 (1.6)	22.1 (11.4)	17.3 (7.9)	15.2 (6.7)	12.1 (5.1)	16.7 (8.9)
Dietary vitamin E (mg)	13.4 (6.8)	11.8 (5.2)	10.0 (4.1)	8.1 (3.4)	5.4 (1.4)	13.6 (6.3)	11.0 (4.9)	9.8 (4.3)	7.8 (3.4)	10.6 (5.3)
Folate (μg)	598 (339)	504 (231)	426 (176)	341 (137)	252 (57)	613 (314)	474 (211)	416 (178)	330 (136)	458 (243)
Fruits (g)	108.4 (115.4)	86.8 (79.7)	70.8 (61.9)	52.8 (46.9)	79.7 (82.7)	150.1 (143.2)	107.0 (88.0)	87.6 (71.9)	62.5 (52.7)	101.8 (100.4)

[a] Number in each column was the same for each baseline characteristic, except for BMI for which it was 11 856 for men and 14 445 for women, height for which it was 12 062 for men and for 14 672 for women, current cigarette smokers for which it was 12 202 for men and 13 728 for women, currently married for which it was 12 438 for men and 15 052 for women, education for which it was 12 405 for men and 15 067 for women, and current hormone replacement therapy for which it was for 8 095 for women.

[b] *One serving* is defined as 67.6 g.

intervals. For each participant, person-years of follow-up were calculated from the study entry to the date of death from stroke, death from any other cause, date on which the person moved out of Takayama City, or the end of the study. We referred to the city residential registers to obtain information on subjects who had moved out. We considered an age-adjusted model to assess the risk or death from total stroke and the subtypes of stroke. A multivariate model with adjusting for possible confounders such as age; body mass index (BMI; in kilograms per square meter, in quintiles and missing values); smoking status (current, past, never smoked, or missing status); physical activity (metabolic equivalent per week); reported history of hypertension; education (12 years or more, or less); and intake of total energy, alcohol, dietary fiber, salt, and total fat was also considered to assess the risk of total stroke. The dietary GI, GL, and intake of carbohydrate and rice in grams were analyzed in quartiles. To test for linear trends across categories, we modeled the median of each category. The dietary GL and intake of carbohydrates, rice, and other nutrients used in the model were adjusted for the total energy intake using the regression analysis proposed by Willett [18]. The dietary GI was left as the crude value. By definition, it represented the quality of consumed carbohydrate, but not the quantity; and hence, it was not likely to be confounded by between-person variation in total energy intake. All the analyses were stratified by sex and then additionally stratified by BMI (<23 and ≥23) only to assess the risk of total stroke. The analysis stratified by BMI was limited to the 11 856 men and 14 445 women who reported both height and weight. The interaction term between sex or BMI and each dietary factor was tested in the model. All the statistical analyses were performed with SAS (SAS Institute, Cary, NC).

3. Results

The characteristics of the study participants at the baseline are presented in Table 1. Participants in higher quartiles of dietary GI were more likely to have lower alcohol consumption and were less likely to be current cigarette smokers. Women in the highest dietary GI were more likely to be older and less likely to be educated. With regard to daily food and dietary intake, participants in higher quartiles of dietary GI were more likely to have lower total calorie intake in line with lowered intakes of carbohydrate and other nutrients.

Table 2 shows the association between each dietary factor of interest and the risk of mortality from total stroke. Among men, the risk of total stroke was not clearly associated with the dietary GI, GL, carbohydrate intake, or rice intake.

Table 2
Hazard ratio of death from stroke according to quartiles of dietary GI, energy-adjusted dietary GL, total carbohydrate intake, and rice intake among 12 561 men and 15 301 women in the Takayama study, Japan

	Men					Women				
	Quartile				*P* for trend	Quartile				*P* for trend
	1	2	3	4		1	2	3	4	
GI										
No. of cases	33	32	30	25		12	31	33	51	
Age adjusted	1	0.96 (0.59-1.56)	1.02 (0.62-1.67)	0.82 (0.49-1.37)	.53	1	2.00 (1.03-3.91)	1.85 (0.95-3.59)	2.46 (1.30-4.63)	.01
Multivariate[a]	1	0.97 (0.59-1.60)	0.96 (0.56-1.64)	0.78 (0.41-1.47)	.50	1	1.90 (0.97-3.74)	1.66 (0.83-3.31)	2.09 (1.01-4.31)	.10
P interaction with sex[a]										.12
Energy-adjusted GL										
No. of cases	42	25	24	29		16	31	43	37	
Age adjusted	1	0.55 (0.34-0.91)	0.68 (0.41-1.13)	0.86 (0.54-1.38)	.41	1	1.49 (0.81-2.72)	1.80 (1.01-3.20)	1.71 (0.95-3.07)	.08
Multivariate[a]	1	0.61 (0.36-1.02)	0.81 (0.44-1.49)	1.00 (0.47-2.15)	.66	1	1.36 (0.73-2.53)	1.57 (0.83-2.97)	1.17 (0.51-2.68)	.60
P interaction with sex[a]										.40
Carbohydrate intake										
No. of cases	34	28	27	31		25	24	35	43	
Age adjusted	1	0.72 (0.43-1.18)	0.76 (0.46-1.25)	0.93 (0.57-1.51)	.72	1	0.73 (0.42-1.28)	0.95 (0.57-1.59)	1.10 (0.67-1.80)	.42
Multivariate[a]	1	0.79 (0.47-1.36)	0.95 (0.51-1.78)	1.17 (0.52-2.62)	.87	1	0.71 (0.39-1.27)	0.88 (0.48-1.60)	0.88 (0.39-2.01)	.85
P interaction with sex[a]										.78
Rice intake										
No. of cases	36	43	13	28		14	32	47	34	
Age adjusted	1	1.06 (0.68-1.65)	0.54 (0.29-1.03)	0.92 (0.56-1.51)	.33	1	1.57 (0.84-2.95)	1.42 (0.78-2.60)	1.92 (1.03-3.57)	.06
Multivariate[a]	1	0.95 (0.59-1.52)	0.53 (0.26-1.04)	0.84 (0.43-1.62)	.28	1	1.47 (0.78-2.79)	1.22 (0.62-2.37)	1.37 (0.64-2.94)	.62
P interaction with sex[a]										.66

[a] Adjusted for age; BMI (in quintiles and missing values); smoking status (current, past, never smoker, or status missing); physical activity (metabolic equivalent per week); reported history of hypertension; education (12 years or longer, or not); and intake of total energy, alcohol, dietary fiber, salt, and total fat.