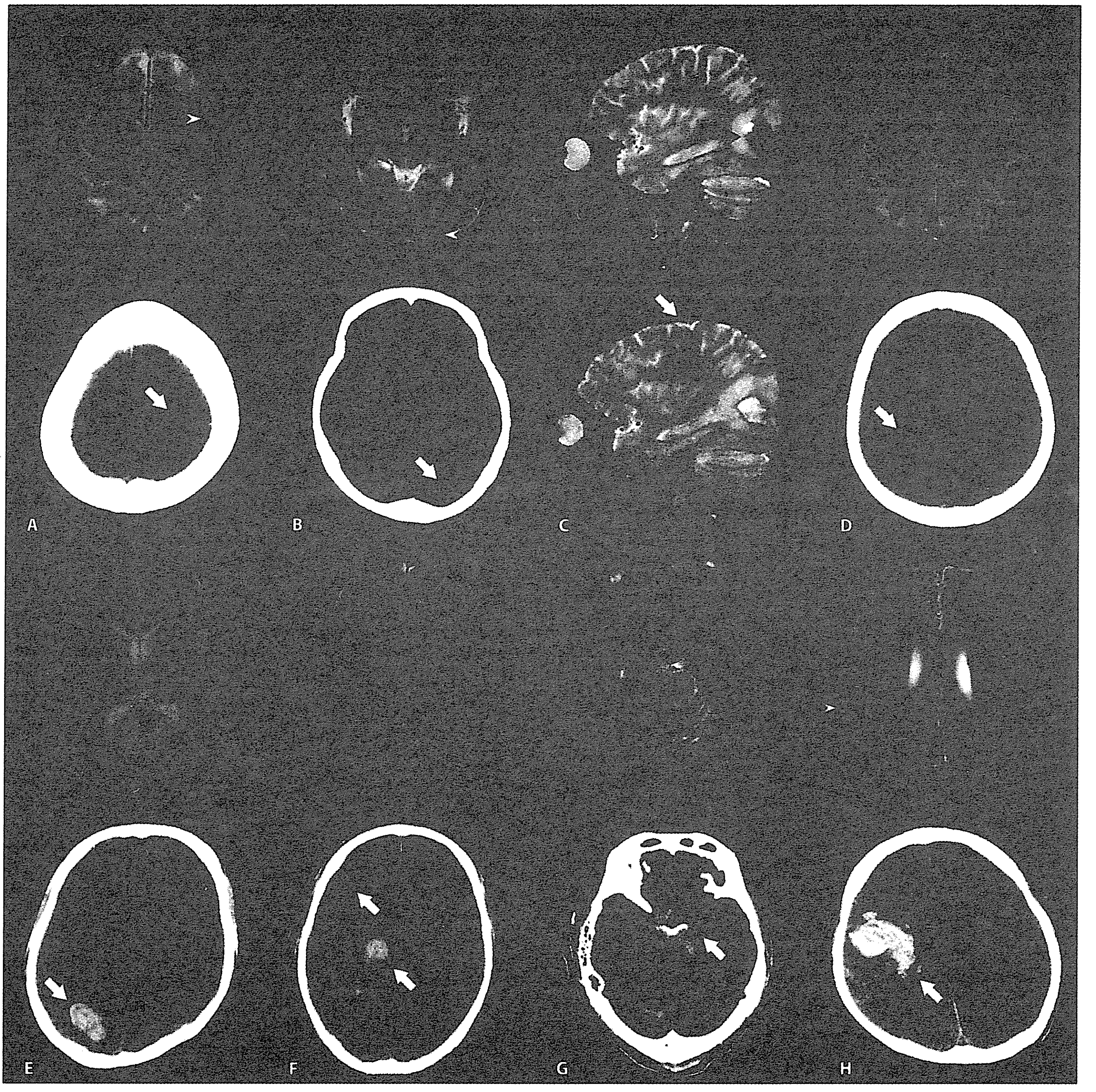

Fig. 1. Location of CMBs and subsequent ICH. **A–H** Initial T2*-weighted MRI and subsequent hemorrhage CT of 8 patients with IE who developed ICH after initial MRI examination. The white arrowhead indicates a microbleed, white arrows a new ICH and black arrows a prior ICH. The hemorrhage lesion seems to coincide with the microbleed in cases **A**, **B** and possibly **H**.

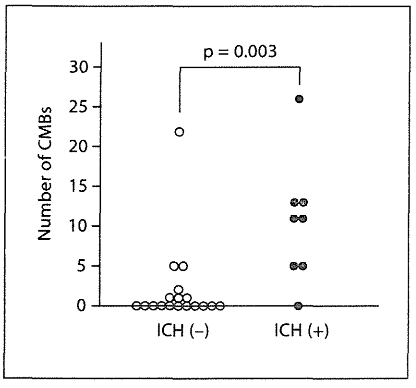

Fig. 2. Number of CMBs and development of ICH. The patients who developed ICH had significantly more CMBs on initial MRI than those without ICH. The p value was calculated by means of the Mann-Whitney U test.

15, ICH in 7 (parenchymal hematoma in 4, subarachnoid hemorrhage in 2 and both in 1), abscess in 1 and aneurysm in 2. CMBs were identified in 14 patients (54%), and 72% of CMBs were present in the lobar region, 12% in the deep region and 16% in the infratentorial region.

Of the 26 patients with MRI on admission, 19 patients presented a new neurological symptom (consciousness disorder in 4, hemiplegia in 6, apraxia in 1, hemianopia in 1 and headache in 7) and underwent subsequent CT or MRI. Subsequently, 8 patients (31%) were diagnosed with symptomatic ICH during the follow-up period. Brain images of these 8 patients are shown in figure 1. Of the other 18 patients without initial MRI, none experienced symptomatic ICH during the follow-up period. Seventeen patients (65%) underwent cardiac surgery within the 3-month follow-up, and 3 experienced the onset of ICH shortly after surgery. The interval between MRI and the onset of ICH in these 8 patients ranged from 1 to 19 days (median 4.5 days). When patients with and without ICH 3 months after MRI examination were compared, significantly more CMBs were observed in the patients who developed ICH (median 11, interquartile range 5–13) compared to those without ICH (median 0, interquartile range 0–1, $p = 0.003$; fig. 2).

Baseline characteristics, including age and hypertension, were not different between the patients with and without the presence of CMBs (data not shown). When patients who developed ICH were compared by univariate analyses (table 1), the presence of preceding ICH [odds ratio (OR) 13.3, 95% confidence interval (CI) 1.7–104] and the presence of CMBs (OR 11.0, 95% CI 1.1–110) were significantly associated with the development of ICH. The number of CMBs was also significantly associated with the development of ICH, and the OR per unit was 1.23 (95% CI 1.06–1.53). Using cutoff values for CMBs of ≥2 and ≥3, the ORs for ICH gradually increased (OR 24.5, 95% CI 2.3–262, and OR 35.0, 95% CI 3.1–399, respectively). When we examined the association between the site of CMBs and the development of ICH, lobar CMBs and infratentorial CMBs were significantly associated with ICH, but deep CMBs showed only borderline significance (table 1).

In multiple logistic regression analyses, the presence of preceding ICH (OR 40.0, 95% CI 2.5–2,870) and the presence of CMBs (OR 34.0, 95% CI 1.3–17,300) were independent predictors of ICH. CMBs ≥2 and ≥3 were also independently associated with the development of ICH, and adjusted ORs for ICH were 42.1 (95% CI 1.9–24,300) and 70.1 (95% CI 2.5–105,000), respectively.

Case Report

A 31-year-old woman with a history of a ventricular septal defect was hospitalized with spike fever and headache. The echocardiogram revealed vegetation on the mitral valve, and multiple blood cultures identified *Streptococcus mutans*, and she was consequently diagnosed as having definite IE. Brain MRI on admission showed multiple small infarctions and CMBs (upper images in fig. 3). Despite intensive antibiotic therapy, she developed severe headache on day 21, and brain CT revealed ICH in the right parietal lobe (fig. 1D). Brain MRI on day 23 showed many new CMBs (lower images in fig. 3). We also performed CT angiography and conventional angiography, but no mycotic aneurysm was identified. She underwent a mitral valve replacement on day 47 and was discharged from hospital on day 61 without sequelae.

Discussion

The development of ICH can be catastrophic and is associated with very poor outcomes in patients with IE. Identifying patients at risk of developing ICH could help determine whether surgical treatment is indicated in patients presenting with IE. We identified a high incidence of impending ICH in patients with IE and CMBs. To the best of our knowledge, this is the first study examining the relationship between CMBs and the development of ICH in patients with IE.

In our study, the incidence of ICH was higher than that reported in previous studies [1, 2, 4]. Brain MRI was performed only in those patients who were potentially at high risk for stroke. When all 44 patients with IE were included

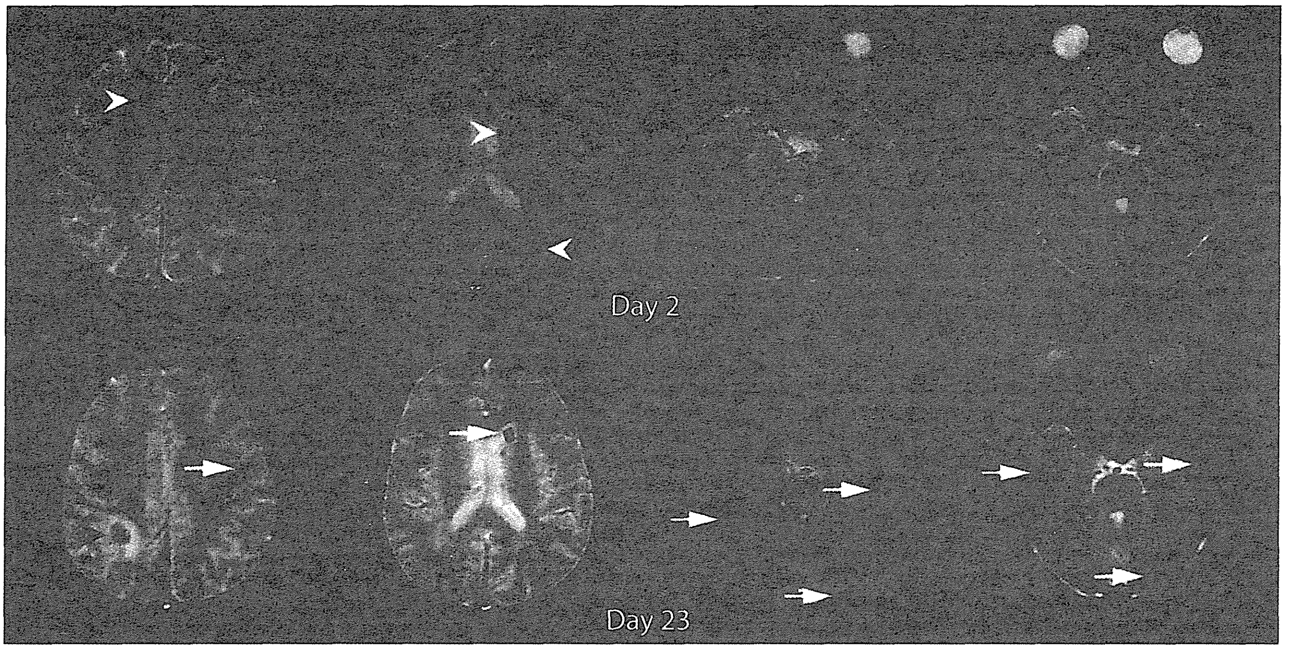

Fig. 3. T2*-weighted gradient echo images of a 31-year-old woman with IE on admission (upper images) and on day 23 (lower images). White arrowheads indicate CMBs on admission, black arrowheads ICH and white arrows new CMBs on day 23.

in the analysis, the incidence of ICH was reduced to 18%. Additionally, our study included more patients with neurological complications than other studies. This also might explain the high incidence of ICH in our study.

CMBs have been reported as a marker of microangiopathy such as hypertensive vasculopathy or cerebral amyloid angiopathy [9, 10], but we found no association between CMBs and hypertension or age. In our study, 72% of CMBs were located in the lobar region. The development of CMBs in patients with IE might represent infectious microangiitis and lead to the development of mycotic aneurysms or pyogenic vasculitis, as has been suggested by previous studies [14, 15]. Unfortunately, none of the patients had undergone a brain MRI before the onset of IE, and we could not identify when the CMBs developed in this study. Whereas the prevalence of CMBs in healthy adults is approximately 5% [16], that in our study was 54%. A similarly high prevalence of CMBs in patients with IE was also reported by Duval et al. [2]. In addition, CMBs can increase rapidly within a short period in patients with IE, as well as after ischemic stroke [17] or cardiac surgery [18], as shown by our case report (fig. 3). These findings lend support to our hypothesis that the development of CMBs is due to IE.

Our study has several limitations. Orders for follow-up CT or MRI were at the discretion of different attending physicians, and it is possible that patients presenting with an abnormal initial MRI may have undergone more follow-up imaging procedures. This could have artificially increased the rate of detection of ICH in patients with preceding ICH or CMBs. Additionally, because of the small sample size, we were unable to subdivide the patients into groups with or without preceding ICH. Although our study indicated that the presence of CMBs was a predictor of ICH independent of preceding ICH, preceding ICH is strongly correlated with both CMBs [9] and recurrent ICH [19]. Further studies are needed to clarify these correlations. Finally, although all patients received appropriate antibiotic therapy in our study, it remains unclear how medical therapy in patients with IE can affect the incidence of ICH.

We showed that the presence of CMBs was an independent predictor of impending ICH in patients with IE. CMBs might represent vascular vulnerability related to IE. Further studies are needed to help establish the value of studies of CMBs for predicting future neurological complications of IE.

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REVIEW ARTICLE

Associations of impaired glucose metabolism and dyslipidemia with cardiovascular diseases: what have we learned from Japanese cohort studies for individualized prevention and treatment?

Yoshihiro Kokubo

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Abstract Metabolic disorder is a modifiable risk factor for cardiovascular diseases (CVD), and lifestyle modification is the key to improving metabolic disorder. Diabetes mellitus has been shown to be a risk factor for coronary heart disease (CHD) and ischemic stroke in both Western and Japanese populations. An association between impaired fasting glucose and pre-hypertension found in an urban Japanese population emphasized the combined risk of CVD. Mean total cholesterol levels in Japan have been increasing in the last three decades. The Japanese evidence for the positive association of total cholesterol with CHD is similar to that in the West. Higher low-density lipoprotein cholesterol (LDL-C) levels pose an increased risk of CHD and atherothrombotic infarction, whereas lower LDL-C levels may pose an increased risk of intracerebral hemorrhage in Japan. Overall, the studies reviewed here show that impaired glucose metabolism and dyslipidemia are emerging risk factors for CVD in the Japanese population.

Keywords Impaired glucose metabolism · Dyslipidemia · Lifestyle · Predictors for cardiovascular disease · Cohort study · Japanese population

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Introduction

Metabolic syndrome comprises a cluster of components of impaired glucose metabolism, abdominal fat accumulation, dyslipidemia, and elevated blood pressure [1]. Each component has been shown to be an independent risk factor for cardiovascular diseases (CVD) in Japanese community cohort studies: impaired fasting glucose [2]; abdominal obesity [3, 4]; low-density lipoprotein cholesterol [5, 6]; and high-normal blood pressure [7–9].

Recently, a new streamlined definition of metabolic syndrome for global populations has been introduced [10]. In this definition, abdominal obesity is just one of the possible components for metabolic syndrome. However, in the Japanese definition of metabolic syndrome, abdominal obesity is an essential component [11]. The definition may mislead a prevention of CVD for non-obesity metabolic disorder, which is a modifiable risk factor for CVD. Changes in lifestyle are the key to improving metabolic disorder, including diabetes mellitus (DM) and dyslipidemia, and thereby to reducing the risk of cardiovascular disease. In this review paper, the focus is on the relation of metabolic symptoms, namely impaired glucose metabolism and dyslipidemia to CVD in the Japanese population.

Impaired glucose metabolism: trends, combination with blood pressure elevation, and individualized preventive approaches

Diabetes mellitus has become a major public health problem [12, 13] as well as a risk factor for mortality [12] and CVD

[14–16]. In Japan, the frequencies of hyperglycemia for 1961, 1974, and 1989 show a trend of increasing incidence: 12.1%, 13.8%, and 31.9% in men and 4.8%, 8.1%, and 27.2% in women, respectively [17].

Previous meta-analysis studies have shown that diabetes is a risk factor for ischemic stroke [18] and coronary artery disease [15, 18, 19]. The Framingham Offspring cohort study showed a positive relationship between impaired fasting glucose and coronary heart disease in women and between diabetes and coronary heart disease in men and women [20]. These results are compatible with those of previous cohort studies in Japan, as described below and summarized in Table 1.

The Hisayama Study indicated that diabetes as defined by the glucose tolerance test was a risk factor for ischemic stroke in men (hazard ratio 2.54; 95% confidence intervals 1.40 to 4.63) and women (hazard ratio 2.02; 95% confidence intervals 1.07 to 3.81) and coronary heart disease in women (hazard ratio 3.46; 95% confidence intervals 1.59 to 7.54) [21]; however, impaired glucose tolerance and impaired fasting glucose were not risk factors for ischemic stroke or coronary heart disease.

In a study of five communities in Japan, diabetes defined by non-fasting glucose levels was a risk factor for non-embolic ischemic stroke in men (hazard ratio 1.8; 95% confidence intervals 1.0 to 3.2) and women (hazard ratio 2.2; 95% confidence intervals 1.2 to 4.0) [22]. This result is similar to that of lacunar infarction. The risk was observed in both non-hypertensive subjects and obese subjects. The positive association was particularly strong in hypertensive subjects with higher skin-fold thickness values (hazard ratio 1.9 and 95% confidence intervals 1.0 to 3.7 for borderline diabetes; hazard ratio 4.9 and 95% confidence intervals 2.5 to 9.5 for diabetes).

A positive association between diabetes and CVD mortality was also observed in a Japanese general population. The

Table 1 Association between blood glucose categories and cardiovascular diseases in Japanese cohort studies

Study name	Number	Sex	Follow-up	End point	Results	Reference
The Suita Study	5321	MF	11.5	Stroke	DM, HR=2.08	[2]
				CHD	IFG, HR=1.46; DM, HR=2.28	
		M		Stroke	DM, HR=1.78	
		F		Stroke	DM, HR=2.66	
				CHD	IFG, HR=1.83; DM, HR=4.32	
The Hisayama Study	2421	M	14	CI	DM, HR=2.15; 2hPG, HR=2.71	[21]
		F		CI	DM, HR=2.10; 2hPG, HR=2.19	
				CHD	DM, HR=3.83; 2hPG, HR=4.44	
Five Japanese communities	4287	M	17	CI	DM, HR=1.8	[22]
				Lacunar infarction	DM, HR=2.1	
	6295	F	17	CI	DM, HR=2.2	
				Lacunar infarction	DM, HR=2.4	
	10582	MF	17	Non-embolic CI	Borderline with non-hypertension, HR=1.7	
					DM: with non-hypertension, HR=1.7	
					DM with higher BMI, HR=2.2	
JPHC study	31,192	MF	12.9	CHD	Borderline HR=1.5	[25]
					DM, HR=2.38	
NIPPON DATA80	9444	MF	17.3	All causes mortality	CBG>=11.1 mmol/L, HR=1.63	[23]
				CVD mortality	5.22 mmol/L<=CBG<7.77 mmol/L, HR=1.22	
					7.77 mmol/L<=CBG<11.1 mmol/L, HR=1.46	
					CBG>=11.1 mmol/L, HR=1.82	
				CHD mortality	7.77 mmol/L<=CBG<11.1 mmol/L, HR=2.43	
					CBG>=11.1 mmol/L, HR=2.62	
The Funagata Diabetes Study	2534	MF	5.7	All cause mortality	ADA 2007: DM, HR=2.11	[24]
				CVD mortality	WHO 1985: IGT, HR=2.3; DM, HR=3.54	
					ADA 2007: DM, HR=3.17	

M men; *F* women; *CHD* coronary heart disease; *CI* cerebral infarction; *CVD* cardiovascular diseases; *DM* diabetes mellitus; *IFG* impaired fasting glucose; *2hPG* 2 h post-loaded glucose levels; *HR* hazard ratio; *BMI* body mass index; *CBG* casual blood glucose; *ADA* American Diabetes Association; *WHO* World Health Organization.

NIPPON DATA 80 Study indicated that high and borderline-high casual blood glucose groups (11.1 mmol/L and 7.77 to 11.1 mmol/L, respectively) had increased risks of coronary heart disease mortality [23]. Similar results were observed for both CVD and all-cause mortality. The Funagata Diabetes Study showed that diabetes defined by both the WHO criteria (1985) and ADA recommendations (1997) were risk factors for all-cause mortality and cardiovascular mortality [24]. However, impaired fasting glucose was not a risk factor for all-cause mortality and cardiovascular mortality. These Japanese cohort studies for mortality risks indicated that diabetes is a risk factor for all-cause and CVD mortality. However, impaired fasting glucose and impaired glucose tolerance may not be risk factors for all-cause or CVD mortality. Further investigations of larger cohort studies are required to clarify these matters.

Recently, the Suita Study showed that impaired fasting glucose is a risk factor for the incidence of cardiovascular disease (hazard ratio 1.49; 95% confidence intervals 1.02 to 2.16) or coronary heart disease (hazard ratio 1.83; 95% confidence intervals 1.01 to 3.32) in women, and that diabetes is a risk factor for stroke in both men (hazard ratio 1.78; 95% confidence intervals 1.00 to 3.12) and women (hazard ratio 2.66; 95% confidence intervals 1.22 to 5.80) and for coronary heart disease in women (hazard ratio 1.78; 95% confidence intervals 1.00 to 3.12) [2]. In addition, compared with normoglycemic and optimal blood pressure Japanese subjects, increased risks of CVD were observed in normoglycemic subjects with high-normal blood pressure or hypertension, impaired fasting glucose subjects with normal or higher blood pressure, and diabetic subjects regardless of blood pressure category (Fig. 1: P-value for interaction=0.046). These two borderline categories may augment the risk of CVD.

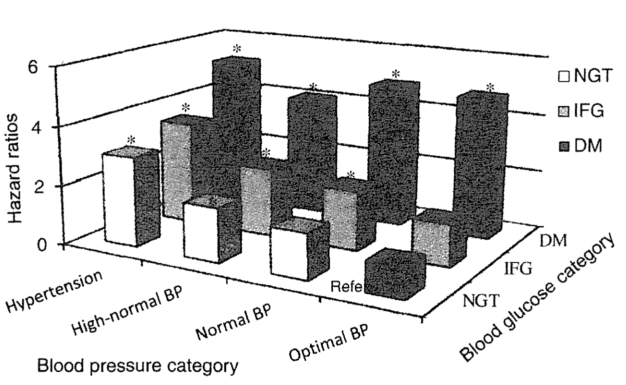

Fig. 1 Multivariable-adjusted hazard ratios of cardiovascular diseases according to the combination of blood pressure and glucose categories. Multivariable-adjusted hazard ratios were adjusting for age, sex, body mass index, smoking, drinking, and hyperlipidemia. *BP* blood pressure; *NGT* normal glycemic tolerance; *IFG* impaired fasting glucose; *DM* diabetes mellitus; *: $P<0.05$ (compared with the optimal blood pressure and normoglycemic group)

In a collaborative meta-analysis of 102 prospective studies from around the world, increased risks of coronary heart disease were observed in unknown diabetic subjects (i.e., subjects with diabetes who are not aware of their disease) with 5.6 to <6.1 mmol/L and 6.1 to <7 mmol/L (hazard ratios [95% confidence intervals]: 1.11 [1.04 to 1.18] and 1.17 [1.08 to 1.26], respectively) [18]. Quite recently, the Japan Public Health Center-based prospective (JPHC) study consisting of a 12.9-year of follow-up for 31,192 individuals aged 40–69 years was observed that diabetes mellitus and hyperglycemia carried an increased risk for coronary heart disease in a Japanese general population [25]. Based on this study and the Suita study [2, 25], both diabetes mellitus and impaired fasting glucose may be a risk factor for the incidence of coronary heart disease in Japan.

In the JPHC study's systematic review of the evidence for pre-diabetes, impaired fasting glucose and impaired glucose tolerance were shown to be associated with modest increases in the risk for CVD [25]. Overall relative risks (95% confidence intervals) for the association between two categories of impaired fasting glucose (100 to 125 mg/dL and 110 to 125 mg/dL) and CVD were 1.18 (1.09 to 1.28) and 1.20 (1.12 to 1.28), respectively. Meanwhile, the risks of CVD for impaired fasting glucose and impaired glucose tolerance were 1.10 (0.98 to 1.23) and 1.20 (1.07 to 1.34), respectively. In two Japanese cohort studies using the oral glucose tolerance test, impaired fasting glucose was not found to pose a risk of CVD [21, 24]. However, in one of these cohort studies, impaired glucose tolerance was observed as a risk of CVD mortality [24]. Larger Japanese cohort studies are required to establish the association between oral glucose tolerance test results and CVD.

In order to prevent CVD, a person with impaired glucose metabolism should eliminate or reduce other cardiovascular risk factors, such as high blood pressure, obesity, smoking, and excess drinking. The Suita study showed that the combination of impaired fasting glucose and high blood pressure greatly increased the risk of cardiovascular disease [2]. Recently, the frequencies of obesity in men and elderly women have increased in Japan [26]. Obesity is a risk factor for impaired glucose metabolism; weight loss reduces the risk of both impaired glucose metabolism [27] and CVD [3].

The average smoking rate in men worldwide has rapidly decreased in recent years, and in 2005 had dropped by 45.5% since its peak. However, the rate in Japan is still higher than that in Western countries [28]. And while, the smoking rate in women is generally lower than that in men. In Japan, the rate for younger women aged 20 to 39 years has increased to around 17 to 20% [28]. Smoking itself is a risk factor for diabetes mellitus [29]. Smoking cessation reduces the risk of both diabetes mellitus [30] and CVD

[31]. Excess drinking is a risk factor for increasing blood pressure [32] and stroke [33]. In order to reduce the risk of CVD, subjects with a combination of two borderline risks, high-normal blood pressure and hyperglycemia, should modify their lifestyles, aiming at cessation of smoking and even moderate drinking, as well as weight reduction if there are overweight or obese.

Dyslipidemia: risks, trends, and individual treatment approaches

According to Japan's National Survey on Circulatory Disorders in 1980, 1990, and 2000, mean levels of total cholesterol increased from 186 mg/dL and 191 mg/dL in 1980 to 200 mg/dL and 208 mg/dL in 2000 among adult men and women, respectively. Frequencies of hypercholesterolemia (total cholesterol levels of 220 mg/dL or more) increased 15% and 19% in 1980 to 27% and 35% in 2000 among men and women, respectively [34]. The difference in mean total cholesterol levels between Japanese and American men was approximately 40 mg/dL in the 1980s. However, this difference had diminished to 15 mg/dL by 1990 and 2000. No changes in mean total cholesterol levels in Japanese or American men aged 60 years and over were observed from 1990 to 2000 [28].

Total cholesterol

A previous meta-analytic study has shown that total cholesterol was positively associated with ischemic heart disease in both middle and old age and at all blood pressure categories [35]. In contrast, the association between total cholesterol and the risk of stroke remains unclear. The Multiple Risk Factor Intervention trial has shown that the risk of death from intracerebral hemorrhage was three times higher in men with serum cholesterol levels under 160 mg/dL than in those with higher cholesterol levels, whereas a positive association was observed between the serum cholesterol level and death from ischemic stroke [36]. A meta-analysis of 45 prospective cohort studies showed no association between blood cholesterol levels and stroke except in those under 45 years of age when screened [37]. The inconsistency in results may be due to the different etiologic origins of stroke. Dyslipidemia may be important for some subtypes of stroke but not for others, because stroke is a heterogeneous disease of various etiologic origins. In American men, an inverse association was observed between the total cholesterol levels and the incidence of intracerebral hemorrhage, while a positive association was observed between total cholesterol levels and the incidence of cerebral infarction [36].

Japanese cohort studies have shown evidence of the positive association of total cholesterol with coronary heart disease similar to that in Western studies. NIPPON DATA80 showed associations between total cholesterol and risk of all-cause mortality (hazard ratio 1.19 and 1.36; 95% confidence intervals, 1.03 to 1.37 and 1.05 to 1.77) in both the lowest (<160 mg/dl) and highest (≥260 mg/dl) total cholesterol groups, respectively [38]. In addition, the hazard ratios of coronary heart disease mortality were 1.4 in the 200 to 219 mg/dL total cholesterol group, 1.7 in the 220 to 239 mg/dL group, 1.8 in the 240 to 259 mg/dL groups, and 3.8 in the 260 mg/dL or above group, compared with the 160 to 179 mg/dL total cholesterol (healthy control) group [38].

LDL cholesterol and non-HDL cholesterol

The Suita Study showed a positive association between serum low-density lipoprotein (LDL) cholesterol and non-high-density lipoprotein (non-HDL) cholesterol levels and increased incidence of myocardial infarction, but not with any type of stroke [6]. The hazard ratio for myocardial infarction was highest in the top quintile of LDL cholesterol (hazard ratio, 3.03; 95% confidence intervals, 1.32 to 6.96) when men and women were combined. The hazard ratio for myocardial infarction was also highest in the top quintile of non-HDL cholesterol (hazard ratio, 2.97; 95% confidence intervals, 1.26 to 6.97). There was no substantial difference in the predictive value for the incidence of myocardial infarction between LDL cholesterol and non-HDL cholesterol. LDL cholesterol can be calculated from fasting blood sample and measurement of total cholesterol, HDL cholesterol, and triglyceride levels from fasting blood samples, according to the Friedewald formula [39]. The formula is not applicable for serum triglyceride levels equal to or greater than ≥400 mg/dL. However, non-HDL cholesterol levels can be easily calculated by routine measured parameters, total and HDL cholesterol without the effect of non-fasting status or hypertriglyceridemia (≥400 mg/dL).

The Hisayama Study showed that the positive association between LDL cholesterol levels and risk of atherothrombotic infarction (P for trend=0.02) and coronary heart disease (P for trend=0.03) remained significant after multivariable adjustment. In the Ibaraki Prefectural Health Study, which was a very large sample consisting of 30,802 men and 60,417 women, high LDL cholesterol levels were associated with an increased risk of mortality from coronary heart disease in men, but not in women [40]. The same study showed that lower LDL cholesterol levels are associated with elevated risk of mortality from intracerebral hemorrhage, but are not associated with increasing risk of cerebral infarction [41]. These Japanese cohort studies suggest that higher levels of LDL cholesterol pose an increased risk of coronary heart disease and possibly atherothrombotic infarction, whereas lower levels of LDL cholesterol may increase the risk of intracerebral hemorrhage.

Recently, the lectin-like oxidized LDL receptor 1 (LOX-1) has been implicated in atherothrombotic diseases [42]. Activation of LOX-1 in humans can be evaluated by use of the LOX index, obtained by multiplying the circulating concentration of LOX-1 ligands containing apolipoprotein B by that of the soluble form of LOX-1. In the Suita Study, higher LOX index values were associated with an increased risk of coronary heart disease [43].

HDL cholesterol

Lower HDL cholesterol predicts coronary heart disease mortality and occurrence of new coronary heart disease events [44]. Elevated total cholesterol was not found to be associated with coronary heart disease mortality in older men, but may be a risk factor for coronary heart disease in older women [44]. The Israeli Ischemic Heart Disease Study showed an independent negative association between HDL cholesterol and ischemic stroke mortality during 21 years of follow-up [45].

Among the Japanese cohort studies, the Oyabe Study demonstrated that lower HDL cholesterol levels were related significantly and independently to an increased risk of all-stroke incidence and ischemic stroke incidence [46]. And in a combined prospective cohort study of 13 urban industrial companies, coronary heart disease incidence was inversely related to HDL cholesterol in Japanese men [47].

Triglyceride

Based on combined data from prospective studies, a high serum triglyceride level is a risk factor for CVD for both men (hazard ratio, 1.32; 95% confidence intervals, 1.26 to 1.39) and women (hazard ratio, 1.76; 95% confidence intervals, 1.50 to 2.07) in the general population, independent of HDL cholesterol [48]. In 26 prospective studies in Asian and Pacific populations, serum triglycerides were an independent predictor of coronary heart disease and stroke risk [49]. In 29 prospective meta-analytic studies in the West, triglyceride levels were moderately associated with coronary heart disease [50].

In Japanese cohort studies, two studies have provided evidence regarding the association between serum triglyceride levels and coronary heart disease and ischemic stroke. A cohort study of four rural communities showed that a high serum triglyceride level was a risk factor for coronary heart disease; even after adjustment for HDL cholesterol levels the significant association remained, although 80% of the baseline participants were non-fasting [51]. The Suita Study has also shown that the risk for ischemic stroke was highest in participants with high triglycerides alone, and that a combination of high serum levels of triglyceride and non-HDL cholesterol was associated with an increased risk of myocardial infarction [52]. High serum levels of triglyceride and non-HDL cholesterol are both important targets for the prevention of CVD, which requires evidence-based guidelines for management in the primary care setting.

Concluding remarks and outlook

This paper reviews the associations of impaired glucose metabolism and dyslipidemia with CVD in Japanese cohort studies. Diabetes mellitus is a risk factor for coronary heart disease and ischemic stroke. Impaired fasting glucose and high-normal blood pressure were shown to be independent risk factors for CVD and coronary heart disease in an urban cohort. The combination of these two borderline categories may increase the risk for CVD. Impaired glucose tolerance has not been observed as a risk factor for the incidence of CVD in Japan. The Japanese evidence for the positive association of total cholesterol with coronary heart disease is similar to that of previous Western studies. Associations with all-cause mortality were observed for both the lower and higher levels of cholesterol: Higher levels of LDL cholesterol have been shown to increase the risk of coronary heart disease and atherothrombotic infarction, whereas lower levels of LDL cholesterol may increase the risk of intracerebral hemorrhage in Japan, as elsewhere. HDL cholesterol levels were inversely related with ischemic stroke. Positive associations between serum triglyceride levels and coronary heart disease and ischemic stroke have also been observed in Japanese populations. The Japanese diet has been rapidly changing in recent decades, as reflected in many of its health indicators such as cholesterol levels, and both impaired glucose metabolism and dyslipidemia are emerging as important risk factors for CVD in the Japanese population. In order to reduce the risk of CVD, subjects with metabolic disorder should reduce other cardiovascular risk factors and improve their lifestyle.

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REVIEW

Traditional risk factor management for stroke: a never-ending challenge for health behaviors of diet and physical activity

Yoshihiro Kokubo

Purpose of review

Recently, many guidelines have given new evidence on the risk factors for stroke. In this review, I refer to the most important guidelines for primary prevention of stroke and hypertension, especially focused on diet and physical activity.

Recent findings

The health behavior recommendations in recent guidelines for the primary prevention of stroke are virtually identical, and the same recommendations appear in the recent guidelines for the management of hypertension, especially with respect to diet and physical activity. The recommended health behaviors consist of weight reduction, reduction of salt intake, increase in fruit and vegetable intake, decrease in saturated and total fat intake (increase in fish intake), physical activity, and moderation of alcohol consumption. Fruits and vegetables have high levels of potassium, antioxidants, phytochemicals, and dietary fiber, and thus are also considered preventive of cardiovascular disease and its risk factors. It was found that individuals with many of these health behaviors have been shown to have a lowered risk of stroke.

Summary

The health behaviors, especially those related to diet and physical activity, appearing in recent guidelines for the management of hypertension are also important for the primary prevention of stroke, and appear in recent stroke guidelines.

Keywords

diet, guidelines, health behavior, physical activity, primary prevention of stroke

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity worldwide [1]. Figure 1 shows the schema of the progression from lifestyle behaviors to the onset of cardiovascular disease (CVD) as follows:

Environmental factor (lifestyle) → risk factors → cardiovascular disease

Environmental and genetic factors are the key factors for the primary stage of preventive CVD. Environmental factors include diet, physical activity, smoking, drinking, mental condition, and socioeconomic factors. Cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, are the key factors for the secondary stage of preventive CVD. It is essential to consider these factors in order to prevent CVD, irrespective of whether lifestyle behaviors and risk factors were improved in the early stage.

Hypertension is the strongest risk factor for CVD worldwide [2,3]. The total population-attributable fractions of high-normal blood pressure and hypertension for CVD were approximately 50% in men and 30% in women [4]. When high blood pressure levels and other risk factors, such as chronic kidney disease [5] or diabetes mellitus [6■], are combined, the risk of cardiovascular disease becomes much

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KEY POINTS

- Reduced intake of sodium and increased intake of potassium.
- Higher consumption of fruits, vegetables, low-fat dairy products and foods reduced in saturated fat (rich in fish and n-3 polyunsaturated fat).
- Increasing physical activity.
- Lifestyle recommendations for primary prevention of stroke are similar to those for preventing hypertension.

higher. The prevention of hypertension is the best way to prevent primary strokes. According to the 2007 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the management of arterial hypertension [7], the Seventh Report of the Joint National Committee (JNC 7) [8], and the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [9], the factors that are effective for the prevention of hypertension are weight reduction, reduction of salt intake, increase in fruit and vegetable intake, decrease in saturated and total fat intake, physical activity, and moderation of alcohol consumption (Table 1). These factors are also considered as preventive for stroke (Table 2).

The Guidelines for the Primary Prevention of Stroke from the American Heart Association/American Stroke Association state that several aspects of diet can contribute to elevated blood pressure: excess salt intake, weight, drinking, and low potassium intake [10■■]. These guidelines also recommend a DASH (Dietary Approaches to Stop Hypertension)-style diet, which emphasizes consumption of fruits, vegetables, and low-fat dairy products. The European Stroke Organization (ESO) guidelines similarly recommend the following measures in order to reduce the risk of stroke: moderate drinking, regular physical activity, maintenance of appropriate weight, and a diet low in salt and saturated fat and rich in fruits, vegetables, and fiber [11]. However, antioxidant vitamin supplements and hormone replacement therapy are not recommended for the primary prevention of stroke in the ESO guidelines [11].

This review will focus on the prevention of stroke events through dietary modifications and increased physical activity, which are never-ending challenges for health behaviors of diet and physical activity.

DIET

Diet is one of the important lifestyle factors for the prevention of stroke, because we habitually eat three times a day. As mentioned in the Introduction, the following dietary factors have been related to stroke prevention: reduction of salt intake, increase in fruit and vegetable intake, and decrease in saturated and total fat intake.

Reduction of salt intake

In the INTERSALT (International Study of Salt and Blood Pressure) study, it is estimated that with a 100 mmol lower daily sodium intake the average decrease in blood pressure from age 25 to 55 would be by 9.0 mmHg for systolic and 4.5 mmHg for diastolic [12]. In Japan, the incidence of stroke is higher than in other countries, partly because both the salt intake and the frequency of hypertension are higher in Japan than in other countries. In a large Japanese general population, sodium intake was increasing associated with mortality from stroke [hazard ratio 1.6, 95% confidence interval (CI) 1.2–2.0], ischemic stroke (hazard ratio 2.0, 95% CI 1.4–2.9), and CVD (hazard ratio 1.4, 95% CI 1.2–1.7) [13].

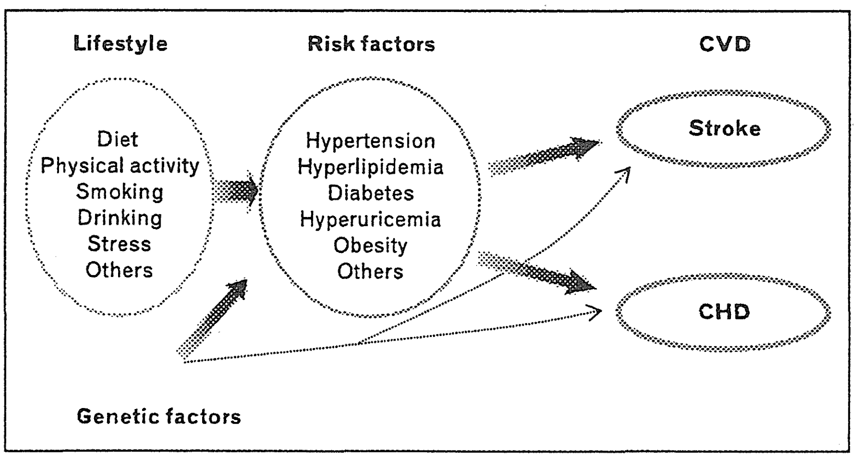

FIGURE 1. Schema of the progression from lifestyle changes to the incidence of cardiovascular disease. CHD, coronary heart disease; CVD, cardiovascular disease.

Table 1. Lifestyle recommendations to prevent hypertension in various guidelines

	JNC 7 [8]	ESC/ESH [7]	JSH 2009 [9]
Weight reduction	Maintain normal body weight	Weight reduction (and weight stabilization)	Maintaining appropriate body weight: BMI <25kg/m^2
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	Increase in fruit and vegetable intake and decrease in saturated and total fat intake	Increased intake of fruits and vegetables. Reduce intake of cholesterol and saturated fatty acids. Increased intake of fish (fish oil)
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day	Reduction of salt intake	Salt restriction to <6 g/day
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 mim per day)	Physical exercise	Exercise: In hypertensive patients with no cardiovascular disease, exercise, which is primarily moderate aerobic exercise, should be performed periodically (for 30 min daily if possible)
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day in men and to no more than 1 drink per day in women and lighter weight men	Reduction of excessive alcohol intake	Restriction of alcohol intake: 20–30 ml/day in men and 10–20 ml/day in women as ethanol
Stop smoking	For overall cardiovascular risk reduction, stop smoking	Smoking cessation	Quitting smoking

Table 2. Lifestyle recommendations to prevent primary stroke in various guidelines

	Guidelines for the primary prevention of stroke: AHA/ASA Guideline [10••]	The European Stroke Initiative recommendations for stroke management [11]
Weight reduction	Among overweight and obese persons, weight reduction is reasonable as a means of reducing risk of stroke	Individuals with an elevated body mass index are recommended to take a weight-reducing diet
Diet and nutrition	Reduced intake of sodium and increased intake of potassium as indicated in the report Dietary Guidelines for Americans are recommended to lower blood pressure	A diet low in salt is recommended
	A DASH-style diet, which emphasizes consumption of fruits, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers blood pressure and is recommended	
	A diet that is rich in fruits and vegetables and thereby high in potassium is beneficial and may lower risk of stroke	A diet low in saturated fat, high in fruit and vegetables and rich in fibre is recommended
Physical activity	Increased physical activity is recommended because it is associated with a reduction in risk of stroke	Regular physical activity is recommended
	Adults should engage in at least 150 min (2 h and 30 min) per week of moderate intensity or 75 min (1 h and 15 min) per week of vigorous intensity aerobic physical activity	

DASH, Dietary Approaches to Stop Hypertension.

Increase in fruit and vegetable intake

Cohort studies have shown that high fruit and vegetable intake reduces stroke incidence and mortality. Two meta-analysis studies reported that fruit and vegetable consumption decreases the risk of stroke [14,15]. The risk reductions of stroke from meta-analysis of seven cohorts were 11% (95% CI 7–15%) for each additional portion per day of fruit and 5% (3–8%) for fruit and vegetables [14]. Those of nine cohorts were 26% (21–31%) for more than five servings per day of fruit and vegetables and 11% (3–17%) for three to five servings per day compared to less than three servings per day [15]. In participants in a large Japanese cohort study, the inverse association between fruit intake and risk was observed only among nonsmokers [16]. Smoking, which causes oxidative stress, diminishes the healthy effects of fruits and vegetables. The mechanism by which high intake of fruits and vegetables prevents stroke may involve the high levels of potassium, antioxidants, phytochemicals, and dietary fiber in these foods, since each of these components has been shown to individually prevent cardiovascular risk factors.

Potassium excretion has been negatively correlated with blood pressure in individuals. A 50 mmol/day lower urinary excretion of potassium has been associated with an average blood pressure increase of 3.4 mmHg systolic or 1.9 mmHg diastolic [12]. A meta-analysis of 33 randomized controlled trials of potassium supplementation showed that the supplementation significantly reduced systolic and diastolic blood pressure. The systolic and diastolic blood pressures were decreased by 4.0 and 2.5 mmHg, respectively, in hypertensive patients, whereas they were decreased by 1.8 and 1.0 mmHg, respectively, in normotensive individuals.

In the US general population, higher potassium intake was associated with lower mortality risk (hazard ratio 0.80, 95% CI 0.67–0.94, per 1000 mg/day of potassium) [17■]. In a pooled meta-analysis of 15 cohorts including 247 510 participants at baseline for 5–19 years of follow-up, a 42 mmol/day higher potassium intake was associated with a 21% lower risk of stroke (hazard ratio 0.79, 95% CI 0.68–0.90) [18■].

Fruits and vegetables are rich sources of antioxidants that may help prevent CVD, including vitamins C and E, carotenoids, polyphenols, and flavonoids. Cohort participants in the top quartiles of baseline plasma vitamin C concentrations had 41–61% lower risk than did those in the bottom quartiles [19–21]. In a Rotterdam cohort study, compared with participants in the lowest tertile of vitamin C intake, those in the second and third tertiles of vitamin C intake had a significantly lower risk of ischemic stroke (hazard ratios 0.69 and 0.66, 95% CIs 0.49–0.98 and 0.46–0.93, respectively) [22]. In another study, a high serum vitamin A concentration was found to have a beneficial effect on early outcome in ischemic stroke [23]. Dietary supplementation with antioxidants including vitamins C, E, and beta-carotene was tested in a meta-analysis of randomized controlled trials, and no significant association with secondary CVD prevention was observed [24].

Flavonoids are a large group of polyphenolic compounds abundant in vegetables, fruits, tea, and red wine, and may contribute to the protective effect of these foods. There are five subclasses of flavonoids, that is, flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins, which have been estimated to contribute to daily dietary intake and thus potentially have effects on health [25]. In a cohort study, Finnish men in the highest quartile of flavonol and flavan-3-ol intake had a relative risk of 0.55 (95% CI 0.31–0.99) and 0.59 (0.30–1.14) for ischemic stroke, respectively, as compared with the lowest quartile [26]. In a Japanese cohort study, green tea consumption of five or more cups per day was associated with a relative risk of 0.88 (95% CI 0.79–0.98) for ischemic stroke compared with less than one cup per day [27]. Recent cohort studies have shown that coffee consumption is protective of stroke. The relative risks of total stroke in Swedish women were 1.00 (reference), 0.78 (95% CI 0.66–0.91), 0.75 (95% CI 0.64–0.88), and 0.77 (95% CI 0.63–0.92) for coffee consumption of less than 1 cup/day, 1–2 cups/day, 3–4 cups/day, and at least 5 cups/day, respectively [28].

Many studies on the intake of soy, a food rich in isoflavones, have reported an impact on decreasing plasma cholesterol levels [29,30]. However, only a few studies exist on the impact of soy intake on CVD, because the average soy intake in Japanese is 10–70 times higher than that in Western people [31,32]. A prospective study of Dutch women did not support the idea that dietary isoflavones lowered the risk of CVD [32]. The quantity of isoflavones consumed by Dutch women, however, was quite small [32]. A prospective study of Japanese men and women showed that soy intake was weakly and inversely associated with total mortality but not mortality due to CVD [33]. Recently, a Japanese community-based prospective study with 40 462 participants has shown that high consumption of soy and isoflavones was associated with a reduced risk of incidence and mortality of cerebral and myocardial infarction among women, particularly postmenopausal women [34]. This study suggests that the consumption of dietary isoflavones and soy intake may be beneficial to postmenopausal women for the prevention of ischemic CVD.

Population cohort studies have revealed dietary fiber, consisting of water-soluble and water-insoluble fiber, to be inversely associated with the risks of coronary heart disease (CHD) [35,36■■] and of stroke [37]. Water-soluble fiber may result in an improvement of glycemic control and a lowering of triglyceride levels [38], as well as a cholesterol-lowering effect [39], especially on low-density lipoprotein cholesterol. Insoluble fiber may slow the intestinal absorption of foods and reduce the levels of clotting factors [40], fibrinolysis [41], coagulation [42], and inflammatory markers [43]. Recently, a relatively large Japanese population-based prospective study has shown higher dietary intakes of total and insoluble fiber to be associated with reduced risk of total strokes, cerebral infarction and intracerebral hemorrhage in women [44■]. The inverse associations between dietary total fiber intake and cardiovascular diseases were statistically significant only for nonsmoking men and women, but not for smoking men and women.

Fish and n-3 polyunsaturated fat (decrease in saturated and total fat intake)

In two large Japanese community samples, dietary intake of fish and n-3 polyunsaturated fatty acid was inversely associated with incidence of CHD [45] and mortality of CVD [46]. However, the association between intake of fat and stroke is controversial. A meta-analysis of randomized controlled trials showed no effects of n-3 fatty acids on cardiovascular events [47]. A large cohort study in men in the US did not show an increase in the risk of ischemic stroke according to dietary intakes of total fat, animal fat, saturated fat, and vegetable fat [48]. The estimated level of association between dairy intake and stroke events pooled from seven prospective studies was not statistically significant [49■]. In a Japanese cohort, a high consumption of animal fat and cholesterol was associated with a reduced risk of cerebral infarction death, whereas those relationships have been diminished in Western counties [50], where the animal product intake is higher than in Japan.

Interestingly, an increased concentration in serum of n-3 polyunsaturated fatty acids, especially docosahexaenoic acid, a marker of fish or fish oil consumption, may protect against atrial fibrillation according to a prospective population-based study [51,52]. Atrial fibrillation is a strong risk factor for cerebral infarction [53]. Therefore, an increased concentration of n-3 polyunsaturated fatty acids may be of benefit for the prevention of cerebral infarction, especially cardio-embolism infarction.

PHYSICAL ACTIVITY

The 2008 Physical Activity Guidelines for Americans include an extensive review of the literature and concludes that individuals engaged in physical activity have a 25–30% lower risk of stroke than inactive individuals [54■,55]. In another study, moderate activity was associated with a lower risk of stroke compared with inactivity (hazard ratio 0.80, 95% CI 0.74–0.86) [56]. This association was mediated through beneficial effects on body weight, blood pressure, serum total cholesterol levels, and glucose levels. The 2008 Physical Activity Guidelines for Americans recommended that adults should engage in at least 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate and vigorous-intensity aerobic activity [10■■,54■].

According to the Physical Activity Guideline for Older Adults [57■], to promote and maintain health, older adults should participate in moderate-intensity aerobic activity for at least 30 min on 5 days of the week, or vigorous-intensity aerobic activity for at least 20 min on 3 days of the week [58]. Even in older adults with chronic illnesses or disabilities, significant health benefits can be obtained by daily nonstrenuous physical activity, such as stretching exercises [55].

Physical activity in leisure time (2–5 h per week) has been significantly associated with a reduced severity of ischemic stroke at admission [59]. Japanese individuals who reported the highest level of physical activity (i.e. walking 1 h/day) had lower mortality of stroke than did those in the second lowest physical activity category (i.e. walking 0.5 h/day) (hazard ratio 0.71, 95% CI 0.54–0.94). [60]

COMBINED IMPACT OF HEALTH BEHAVIORS

In the above mentioned guidelines for the primary prevention of stroke, there is a study on health behaviors for the prevention of stroke, with a focus on diet and physical activity [61]. This prospective population study (20 040 men and women aged 40–79 at baseline) reported on the potential combined impact of four health behaviors, that is current nonsmoking, physical inactivity, moderate alcohol intake, and plasma concentration of vitamin C at least 50 μmol/l (indicating fruit and vegetable intake of at least five servings a day), on incidence of stroke. The relative risks for stroke were 1.15 (95% CI 0.89–

1.49) for three health behaviors, 1.58 (1.22–2.05) for two, 2.18 (1.63–2.92) for one, and 2.31 (1.33–4.02) for none ($P<0.001$ for trend), compared with people with all four health behaviors.

CONCLUSION

The health behavior recommendations in guidelines for the primary prevention of stroke are highly similar, and the same recommendations appear in the guidelines for the management of hypertension, especially with respect to diet and physical activity. The recommended health behaviors consist of weight reduction, reduction of salt intake, increase in fruit and vegetable intake, decrease in saturated and total fat intake, physical activity, and moderation of alcohol consumption. Individuals with many of these health behaviors were found to be at lower risk of stroke.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 96–97).

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Silent Cerebral Infarcts and Cerebral White Matter Lesions in Patients with Nonvalvular Atrial Fibrillation

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Background: Nonvalvular atrial fibrillation (NVAF) is a well-known strong risk factor for stroke, although few studies have examined silent cerebral ischemic lesions in patients with NVAF. We investigated silent cerebral infarcts (SCIs) and cerebral white matter lesions and risk factors for stroke in NVAF patients. *Methods:* Subjects included 71 consecutive patients with NVAF and 71 sex-and age-matched controls with sinus rhythm who had undergone MRI. Number, size, and localization of SCIs and severity of periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH) on magnetic resonance imaging were analyzed. The risk factors and CHADS2 score for stroke were also investigated. *Results:* The number of SCIs was significantly larger and the rates of SCIs in the cortex/subcortex and deep white matter were higher in the NVAF group than in the control group. The DSWMH grade was also significantly higher in the NVAF group. NVAF was an independent risk factor for SCIs and DSWMH. The number of cortical and subcortical SCIs was significantly correlated with CHADS2 score. *Conclusions:* Cortical/subcortical and deep white matter SCIs were more frequent and DSWMH grades were higher in NVAF patients compared with control subjects. CHADS2 score was an effective scheme not only in stroke risk but also in risk of SCI. **Key Words:** Atrial fibrillation—silent brain infarction—cerebral white matter lesion—maginetic resonance imaging.

Silent cerebral infarcts (SCIs) and cerebral white matter lesions with no obvious neurologic symptoms appear from middle age onward, and their frequency tends to increase with advancing age.[1] Both types of lesion, if present in large numbers, have been shown to result in progressive decline of cognitive function[2,3] and psychological symptoms, such as depression.[4] A high probability of future stroke has also been reported in individuals with these lesions.[5]

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A pathologic study in Hisayama, Japan showed that SCIs are frequently observed in the subcortex, and that age, hypertension, and atrial fibrillation are significant risk factors for SCIs.[6] Cerebral white matter lesions are categorized into periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH). Age[7] and hypertension[8] have previously been identified as risk factors for these lesions, and they are also believed to be the result of impairment in the cerebral arterioles.[9]

There have been several previous reports of research on nonvalvular atrial fibrillation (NVAF) and SCIs, and it has been reported that not only cerebral embolism but also SCIs are likely to occur in NVAF patients,[10,11] although only few studies have addressed the relationship of NVAF with SCIs and cerebral white matter lesions. In this study, we investigated the characteristics of cerebral white matter lesions without neurologic symptoms and SCIs on magnetic resonance imaging (MRI) and also investigated the relationship of these lesions with risk factors for stroke in NVAF patients and non-NVAF patient controls.

The CHADS2 score is widely used for risk stratification in NVAF patients; the score includes *c*ongestive heart failure, *h*ypertension, *a*ge over 75 years, *d*iabetes mellitus, and history of *s*troke or transient ischemic attack (TIA) as risk factors for stroke.[12,13] However, the usefulness of the scheme in Japanese patients has not been adequately clarified. In our study, the association of CHADS2 score with SCIs in NVAF patients was also examined.

Methods

The subjects were patients who had attended or were admitted to our hospital between 2003 and 2007. All patients in our study had undergone cranial MRI.

The NVAF group consisted of 71 consecutive patients (48 males, 23 females; average age, 74.4 ± 9.9 years) with chronic atrial fibrillation (29 patients) or documented paroxysmal atrial fibrillation (42 patients), excluding those with atrial fibrillation associated with valvular disease.

The control group consisted of 71 consecutively sex- and age-matched patients (48 males, 23 females; average age, 73.7 ± 8.2 years) with sinus rhythm who had been examined in our department during the same period and who did not have any central nervous system involvements.

No patients in either group had a history of stroke or TIA, and patients with known neurologic disorders were excluded. The control group did include patients with subjective symptoms alone, such as headache, dizziness, tinnitus, and tingling of the hands or feet.

MRI was performed using a 1.5-T system device that visualized T1- or T2-weighted MRI images in 7-mm slices with gaps of 0.50 mm parallel to the orbitomeatal (OM) line. MRI was conducted according to the following conditions: standard axial T1 (TR, 425-510 ms; TE, 12-13ms), standard axial T2 (TR, 3000-3247 ms; TE, 90-122 ms), with a field of view 220 × 220. Scattered, irregularly shaped lesions of diameter ≥3 mm presenting as T2 high-intensity and T1 low-intensity findings on horizontal sections were regarded as SCIs. Lesions <3 mm were excluded because there was a high possibility to include dilatation of the perivascular space, demyelination, or gliosis.[14]

Previous reports have stated that among subcortical small infarcts, cerebral infarcts with a diameter ≥5 mm are more likely to be associated with atherosclerosis of major arteries and platelet activation than those with a diameter <5 mm.[15] Therefore, in this study, the size of the infarct area was classified as either 3 to 5 mm or >5 mm. The number of SCIs was classified into 1 of 3 categories: "0," "1-2," or "≥3." Localization of ischemic lesions visible on MRI was classified into 1 of the following 5 categories: cortex/subcortex, deep white matter, thalamus/basal ganglia, brain stem, and cerebellum.

Cerebral white matter lesions were classified into PVH and DSWMH according to the classification of Fazekas.[16] PVH was categorized as: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; and grade 3, irregular PVH extending into deep white matter. DSWMH was categorized as: grade 0, absent; grade 1, punctuate foci; grade 2, beginning confluence of foci; and grade 3, large confluent areas.

All images were shuffled before evaluation and interpreted by multiple neurologists and neuroradiologists who were blinded to the clinical data. The final diagnosis of each MRI lesion was made by consensus.

We also investigated the relationships with vascular risk factors (hypertension, hypercholesterolemia, diabetes, cigarette smoking, and alcohol drinking), body mass index (BMI), maximum intima-media thickness (max IMT) of the carotid artery measured by high resolution duplex ultrasonography, left atrial diameter (LAD) measured by transthoracic echocardiography, blood coagulation markers (thrombin-antithrombin III complex [TAT], and D-dimer), platelet activation marker (β-thromboglobulin [β-TG]), which were quantitated using enzyme immunoassay, and the CHADS2 score.

Hypertension was defined as blood pressure ≥140/90 mm Hg, an obvious history of hypertension, or a history of drug treatment. Diabetes was defined as HbA1c ≥6.0%, an obvious history of diabetes, or a history of drug treatment. Hypercholesterolemia was regarded as total serum cholesterol ≥220 mg/dL, an obvious history of hypercholesterolemia, or a history of drug treatment.

Smoking was considered habitual if the patient had a history of smoking at least 20 cigarettes a day for at least 1 year. Drinking was considered habitual if the patient had consumed at least 30 g of alcohol a day for at least 1 year.

The CHADS2 score is a risk stratification system for NVAF patients.[13] Scores of 0 to 6 points are determined based on the following factors: *c*ongestive heart failure (1 point); *h*ypertension (1 point); *a*ge over 75 years (1 point); *d*iabetes mellitus (1 point); and previous *s*troke or TIA (2 points).

Statistical analyses were performed using SAS (version 9.0; SAS Institute; Cary, NC), with $P < .05$ being statistically significant. The Student t and Mann–Whitney U tests were used to compare ages, numbers of SCIs, and test values between the 2 groups, and the Chi-square test was used to compare risk factors with the prevalence of SCIs and cerebral white matter lesions. Age, sex, hypertension, hypercholesterolemia, diabetes, NAVF, and aspirin intake were also analyzed as independent risk factors for MRI lesions using a multiple logistic regression analysis. The association of CHADS2 score with number of SCIs in NVAF patients was examined using the Spearman correlation analysis. Age and test values were all expressed as means ± standard deviations (SD). Differences at $P < .05$ were considered significant for all results.