dysregulation of blood pressure is the following: Kawano et al [31] reported that hyperglycemia after OGTT suppresses flow-mediated endothelium-dependent vasodilation of brachial artery in the impaired–glucose tolerance group and the diabetic group. They also demonstrated that the endothelial function decreased in association with an increase in plasma levels of TBARS after OGTT [31]. The current study might result in dysregulated blood pressure through endothelial dysfunction in the group of WC ≥85 because of increased reactive oxygen species production after OGTT (Fig. 1I). These vasodilation responses of the brachial arteries in 1- and 2-hour post-OGTT need to be investigated in the further study.

The current guidelines of the World Health Organization stipulate a target 2-hour postprandial (postglucose challenge) plasma glucose level of less than ,140 mg/dL [32]. The OGTT is helpful in screening for postprandial hyperinsulinemia, prediabetes, and diabetes. Standardized and validated protocols for assessment of postprandial dysregulated metabolism including blood pressure and TG levels are not yet available; and thus, normal values are not well defined at this stage. Ogita et al [30] reported that the changes in serum TG levels after OGTT are different from those after an oral fat tolerance test regarding the changes in plasma levels of insulin and apolipoprotein B. Sometimes, these tests are criticized as unrealistic methods for determination of postprandial metabolism because we scarcely consume glucose only or fat only. Therefore, analyses of the postprandial changes using various tolerance tests are required in the future.

Oxidative stress, defined as dysregulation of the cellular redox state, plays a pivotal role in the pathogenesis of vascular failure, especially vascular endothelial dysfunction [33,34]. Recent reports have demonstrated that the pathophysiology of postprandial dysregulated metabolism, especially hyperglycemia, was characterized by hyperglycemic spikes that induce oxidative stress [35,36]. To our knowledge, the effect of glucose loading on serum oxidative stress levels has not been firmly characterized previously. We therefore assessed the oxidative stress response to OGTT in both control subjects and subjects with abdominal obesity, that is, the WC ≥85 group. The present study showed that %TBARS after OGTT was −10.8% ± 5.3% in the WC <85 group (Fig. 1I), partly because the levels of TG and blood pressure, which are known to correlate with oxidative stress [37], decreased in the WC <85 group after the glucose load (vs baseline: $P = .07$, Fig. 1I). However, in the WC ≥85 group, the percentage change in TBARS was 3.3% ± 3.4%; that is, oxidative stress did not decrease but rather increased in subjects with abdominal obesity in response to glucose overload (Fig. 1I). This may be explained at least in part by overproduction of oxidative stress by accumulated visceral fat, as we reported previously [19]. The sustained increase in oxidative stress might accelerate vascular damage, that is, increased max IMT observed in the WC ≥85 group (Table 1).

Adiponectin is an adipocyte-specific secretory protein with antiatherosclerotic and antidiabetic properties in experimental studies [17]. Blood adiponectin levels are low in obesity [18]. In the present study, we found that subjects with abdominal obesity had lower blood levels of adiponectin in the fasting state before the OGTT compared with those without such obesity (Table 1), as reported previously [18]. Yildiz et al [38] reported no significant differences in 24-hour adiponectin patterns between lean and obese subjects. Furthermore, Yamauchi et al [39] reported that 75-g OGTT did not alter serum adiponectin levels in healthy subjects. It has been also shown that plasma adiponectin levels after a meal increase in obese subjects but not in lean subjects [40]. Experimental studies showed that adiponectin gene expression is reversibly down-regulated by insulin [41]. However, the present study demonstrated that there was no significant difference in %adiponectin during an OGTT between subjects with and without abdominal obesity (Fig. 1H). Differences in age, sex, body fat, disease, or the test among studies may account for the discrepant findings. This pathophysiologic relevance should be further investigated in a large number of subjects.

Treatment of postprandial metabolic dysregulation in subjects with abdominal obesity could include visceral fat reduction by diet and exercise, and various pharmacologic agents, which could probably lead to improvement of prognosis of atherosclerotic disease. Future prospective randomized controlled trials are needed to establish postprandial metabolism as an independent cardiovascular risk factor and confirm that intervention for postprandial metabolic dysregulation can improve cardiovascular prognosis.

In conclusion, the present study demonstrated a different response of blood pressure and glucose-lipid metabolism after an OGTT in WC ≥85 subjects relative to WC <85 subjects. Even if fasting metabolic parameters remain within the reference range, various loading tests for evaluating postprandial metabolism should be considered to prevent CVDs, especially in subjects with abdominal obesity.

4.1. Limitations of the study

Our study had several limitations. First, the cross-sectional design makes it difficult to establish a cause-effect relationship. Second, the results may not be valid in non-Japanese populations. Third, we used WC to evaluate abdominal obesity in the present study; and further research on both visceral and subcutaneous fat areas measured by computed tomography is needed to clarify the effects of visceral and subcutaneous adiposity on metabolic dysregulation. Fourth, serum lipid metabolism, adiponectin, and TBARS concentrations were measured in the fasting state before an OGTT and at 120 minutes after an OGTT, but not at 30 and 60 minutes after an OGTT. Measurement at each time point after an OGTT should be performed for a better assessment of the postprandial phenomenon. Finally, it was

difficult to recruit a sufficient number of control subjects; and thus, further multicenter studies of larger samples should be conducted in the future.

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Relationship between visceral fat accumulation and urinary albumin-creatinine ratio in middle-aged Japanese men

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ABSTRACT

Objective: Chronic kidney disease including microalbuminuria relates to cardiovascular disease (CVD). Microalbuminuria is also known to be a marker of generalized endothelial dysfunction. The metabolic syndrome which encompasses visceral fat accumulation and various metabolic disorders, has also an increase in albuminuria and relates to CVD. However, the relationship between visceral fat accumulation and albuminuria remains to be defined. The present study investigated the relationship between visceral fat accumulation and urinary albumin-creatinine ratio (UACR) in Japanese men.

Methods: This study group comprised 1990 Japanese male subjects, who were employees of a city office, had undergone annual health check-up. Urinary albumin was collected from a single spot urine specimen collected anytime between morning and afternoon. Visceral fat area was estimated (eVFA) by the bioelectrical impedance analysis method.

Results: Log-UACR correlated with age, log-body mass index (BMI), log-waist circumference (WC), log-eVFA, log-adiponectin, blood pressure, serum lipids and hemoglobin A1c (HbA1c). Stepwise multiple regression analysis identified log-eVFA, as well as HbA1c, blood pressure, log-TG, and age, as a significant determinant of log-UACR. Moreover, subjects with eVFA $\geq 100\,cm^2$ had significantly higher UACR than those with eVFA $<100\,cm^2$, irrespective of BMI. UACR was significantly worse in subjects with high numbers of metabolic risk factors, and moreover in subjects with eVFA $\geq 100\,cm^2$ than in those with eVFA $<100\,cm^2$.

Conclusion: These results suggested that visceral fat accumulation is associated with an increase in UACR. Evaluation of both visceral fat accumulation and urinary albumin may be important for preventing atherosclerotic diseases.

1. Introduction

Metabolic dysfunctions contribute to endothelial dysfunction and, subsequently, to accelerated atherosclerosis [1]. Chronic kidney disease (CKD) and microalbuminuria have recently been recognized as a risk factor for cardiovascular disease (CVD) [2,3]. Albuminuria, resulting from leakage of albumin across the glomerular podocyte filtration barrier into the urine, is also known to be a marker of generalized endothelial dysfunction [4]. It is also known to that subjects with the metabolic syndrome (MetS) have often microalbuminuria [5].

Accumulation of visceral fat is an important component of the MetS; which encompasses various metabolic disorders such as glucose intolerance, dyslipidemia and hypertension, and is associated with atherosclerotic cardiovascular diseases [6]. We have measured visceral fat area (VFA) in large-scale general population using the non-invasively bioelectrical impedance analysis (BIA) method [7]. We reported previously the relationship between visceral fat accumulation and cardiovascular-related risk factor accumulation in middle-aged men [8]. Adiponectin, which was identified by our group as an adipocytokine in the human adipose tissue cDNA library [9], is a key molecule in the development of cardiovascular disease related to the MetS [10]. We also reported recently the

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relationship between visceral fat accumulation and adiponectin in Japanese general population [11]. In addition, recent reports have suggested that the MetS might be an important factor in the pathophysiology of CKD [12]. However, the relationship between visceral fat accumulation and urinary albumin-creatinine ratio (UACR) remains to be defined.

The aim of the present study was to define the relationship between visceral fat accumulation and urinary albumin excretion in middle-aged Japanese male subjects.

2. Subjects and methods

2.1. Subjects

This study group comprised 1990 Japanese male workers, who were employees of Amagasaki city office, Hyogo; an urban area, and had undergone annual health check-up in year 2006. Accordingly, 1990 men (age, 20–68 years, mean ± SD; 48.0 ± 10.5 years, body mass index (BMI), 15.6–42.9 kg/m^2, mean ± SD; 24.0 ± 3.0 kg/m^2), were enrolled. The study was approved by the human ethics committee of Osaka University and a written informed consent was obtained from each participant. This trial (called The Amagasaki Visceral Fat Study) is registered with University hospital Medical Information Network, number UMIN 000002391.

2.2. Anthropometric data

Anthropometric variables (height, weight and waist circumference (WC)) were measured in standing position. BMI was calculated as weight (in kg) divided by the square of height in meters (m^2). WC at the umbilical level was measured with a non-stretchable tape in the late exhalation phase while standing (in cm). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the sitting position to the nearest mmHg. Visceral fat area (VFA) was estimated by the BIA method, as reported previously by our group [7]. Briefly, the voltage recorded at the flank to the flow of current between the umbilicus and the back correlates significantly with VFA and is not influenced by the amount of subcutaneous fat. We demonstrated previously that VFA estimated by BIA (eVFA) correlates significantly with that determined by computed tomography (CT) [7]. The coefficient of variation of BIA for the value of CT was 0.89% in the standing posture and late exhalation.

2.3. Laboratory measurements and definition of number of risk factors

Venous blood samples were collected for measurements of blood glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), Hemoglobin A1c (HbA1c), uric acid, and adiponectin while the subject was in the sitting position. UACR was calculated from a single spot urine specimen collected anytime between morning and afternoon. Urine albumin concentration was determined by immunoturbidimetric method (N-assay TIA MicroAlb, Nittobo Medical, Japan). Since we have to study a large number of subjects within a limited period of time in the office, i.e., work environment, food intake on the day of the annual health check-up was left at the discretion of the individual. Serum concentrations of adiponectin were measured by a latex particle - enhanced turbidimetric assay (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan and Mitsubishi Chemical Medience, Tokyo, Japan) [13]. The within-run and total coefficient of variation for this assay are 0.8–1.9% and 1.1–2.0%, respectively, and the results correlated significantly with enzyme-linked immunosorbent assay-based methods (R = 0.99). The measurement of VFA by BIA and serum adiponectin concentration complied with the Guidelines of the Ethical Committees of Osaka University. Informed consent was obtained from all subjects.

We examined the presence/absence of three metabolic risk factors: elevated blood pressure (SBP ≥130 mmHg and/or DBP ≥85 mmHg), dyslipidemia and dysglycemia/impaired glucose tolerance. Dyslipidemia represented hypertriglycemia (fasting or postprandial TG ≥1.69 or 2.27 mmol/L [14], respectively, and/or HDL-C <1.04 mmol/L). Dysglycemia/impaired glucose tolerance represented hyperglycemia (fasting or postprandial plasma glucose concentration ≥6.1 or ≥7.77 mmol/L [15], respectively). The subjects received treatment for these conditions were considered positive for that factor.

2.4. Statistical analyses

Data of UACR, BMI, WC, eVFA, adiponectin and TG levels showed skewed distribution, and were therefore log-transformed before analysis. Pearson's correlation coefficient was used to examine the relationship between log-UACR and various metabolic parameters (Table 2). Stepwise multiple regression analysis was conducted to identify those parameters that significantly contributed to log-UACR (Table 3). Parameters with F value >4.0 were subsequently entered into the regression analysis as independent variables. The relationship between UACR and number of risk factors and eVFA were analyzed by Kruskal–Wallis test (Fig. 2). Significant level was set at $p < 0.05$. Continuous variables were expressed as mean ± SEM (Figure) or SD (Table). All statistical analyses were performed with Stat View-J 5.0 (Statistical Analysis System Inc., Cary, NC).

3. Results

3.1. Characteristics of male subjects enrolled in the present study

Visceral fat accumulation was defined as VFA of ≥100 cm^2 [16]. The number of subjects with visceral fat accumulation and the distribution of UACR in the current study are shown in Table 1. In the present study, 42.5% (n = 845/1,990) had visceral fat accumulation (eVFA >100 cm^2). For UACR, 84.9% had UACR <10 mg/g creatinine, 4.0% had ≥30 to <300 mg/g creatinine, and only 0.3% had ≥300 mg/g creatinine. These results for the distribution of UACR were similar to previous report in general population [3].

With regard to the smoking status, 39.6% of the subjects were current smokers, whereas 44.1% were non-smokers. The subjects who were current smokers had significantly higher UACR (13.7 ± 1.5 mg/g creatinine) than non-smokers (7.8 ± 0.6 mg/g creatinine) and ex-smokers (7.7 ± 1.1 mg/g creatinine) (current smokers versus non-smokers; $p < 0.001$, versus ex-smokers; $p < 0.05$). Moreover, there was a significant correlation between Log-UACR and Brinkman index (daily number of cigarettes × years) in male current smokers (r = 0.4123, p = 0.0002, data not shown).

3.2. Relationship between UACR and metabolic parameters

Table 2 lists the correlation coefficients for the relationship between UACR and various metabolic parameters. Since each of six parameters, such as UACR, BMI, WC, eVFA, adiponectin and TG, showed non-Gaussian skewed distribution, they were log-transformed before analysis. Log-UACR correlated positively with age, log-BMI, log-WC, log-eVFA, SBP, DBP, TC, log-TG, HbA1c and uric acid, and negatively with log-adiponectin and HDL-C. However, there was no correlation between log-UACR and LDL-C, cratinine and estimated-glomerular filtration rate (eGFR, Modification of Diet in Renal Disease (MDRD)). Stepwise multiple regression analysis using these data of subjects identified HbA1c, SBP, log-TG, age

Table 1
Baseline characteristics of the studied population.

n (male)	1990
Age (year)	48.0 ± 10.5
Body weight (kg)	68.8 ± 9.6
Body mass index (kg/m^2)	24.0 ± 3.0
Body surface area (m^2)	1.79 ± 0.13
Waist circumference (cm)	83.7 ± 8.4
eVFA (cm^2)	94.5 ± 40.5
<100 (cm^2)	n = 1145 (57.5%)
≥100 (cm^2)	n = 845 (42.5%)
Systolic blood pressure (mmHg)	125.7 ± 15.1
Diastolic blood pressure (mmHg)	76.4 ± 10.8
Total cholesterol (mg/dl)	5.23 ± 0.86
Triglyceride (mg/dL)	1.68 ± 1.38
HDL-chotesterol (mg/dL)	1.43 ± 0.35
LDL-cholesterol (mg/dL)	3.02 ± 0.77
HbA1c (%)	5.2 ± 0.8
Creatinine (mg/dL)	0.88 ± 0.13
Uric acid (mg/dL)	6.1 ± 1.3
UACR (mg/g Creatinine)	10.1 ± 31.3
<10	n = 1690 (84.9%)
≥10 to <30	n = 215 (10.8%)
≥30 to <300	n = 80 (4.0%)
≥300	n = 5 (0.3%)
eGFR (MDRDHmL/mm/1.73m^2)	75.7 ± 12.8
<60	n = 170 (8.5%)
≥60	n = 1820 (91.5%)
Adiponectin (μg/mL)	6.7 ± 3.5
Hypertension	n = 276 (13.9%)
Diabetes mellitus	n = (4.9%)
Dyslipidemia	n = 108 (5.4%)
Cancer	n = 8 (0.4%)
Past history	
Coronary artery disease	n = (1.0%)
Cerebrovascular disease	n = (0.4%)
Smoking	
Current smoker	n = 789 (39.6%)
Ex-smoker	n = 324 (16.3%)
Non-smoker	n = 877 (44.1%)

Data are mean ± SD. Numbers (n) of subjects.
eVFA: estimated visceral fat area. HDL: high-density lipoprotem. LDL: low-density lipoprotem. HhAic: hemogtoiNn Ale. UACR: unnary albumtn-creabnine ratio. eGFR: estimated-glomerular filtration rate. MDRD: Modification of Diet in Renal Disease Hypertension, Diabetes mellitus, Dyslipidemia, under treatments including medications.

Table 2
Correlation between log-UACR and various parameters.

	Univariate	
	r	p value
Age	0.232	<0.0001
Log-BMI	0.187	0.0001
Log-WC	0.239	<0.0001
Log-eVFA	0.217	<0.0001
Log-adiponectin	−0.045	0.0456
SBP	0.248	<0.0001
DBP	0.256	<0.0001
TC	0.063	0.0028
Log-TG	0.187	<0.0001
HDL-C	−0.073	0.0011
LDL-C	0.002	N.S.
HbA1c	0.029	<0.0001
Creatinine	−0.018	N.S.
Uric acid	0.048	0.0309
eGFR (MDRD)	−0.002	N.S.

N.S.: no significant. Pearsons correlation coefficient was used to examine the correlation between log-UACR and each of the listed parameters.

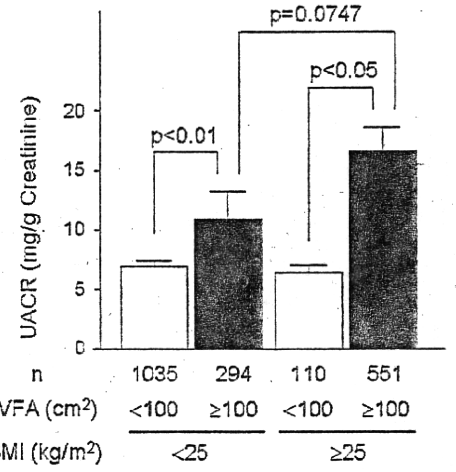

Fig. 1. Relationship between UACR and body fat distribution. Subjects were divided according to body mass index (BMI) using a cutoff value of 25 kg/m^2 and estimated visceral fat area (eVFA) using a cutoff value of 100 cm^2, measured in 2006. Data are mean ± SEM. UACR: urinary albumin-creatinine ratio.

and log-eVFA as significant determinants of log-UACR, but did not log-adiponectin (Table 3).

3.3. Relationship between UACR and obesity-related parameters

We investigated the correlation between UACR and degree of obesity and body fat distribution, such as BMI, WC and eVFA.

First, to clarify whether the degree of obesity or body fat distribution relates more strongly with UACR, we divided subjects into four groups according to BMI (cutoff value 25 kg/m^2) and eVFA (cutoff value 100 cm^2) (Fig. 1). Subjects with eVFA ≥100 cm^2 had significantly higher UACR than those with eVFA <100 cm^2, irrespective of BMI. In the subjects with eVFA ≥100 cm^2, particularly those with BMI ≥25 kg/m^2, tended to have higher UACR than those with BMI <25 kg/m^2. Interestingly, subjects with visceral fat accumulation but without overall obesity (eVFA ≥100 cm^2 plus BMI <25 kg/m^2) had higher UACR than those without visceral fat accumulation but with overall obesity (eVFA <100 cm^2 plus BMI ≥25 kg/m^2). However, the difference was not statistically significant (Fig. 1). Regarding this point, age of the subjects of the two groups was significantly different (BMI <25 kg/m^2; 46.4 ± 0.3 years versus 52.3 ± 0.5 years, $p < 0.0001$, BMI ≥25 kg/m^2; 42.8 ± 1.0 years versus 50.0 ± 0.4 years, $p < 0.0001$, data not shown), which could

Table 3
Results of stepwise multiple regression analysis for log-UACR.

Variable	Regression coefficient	Standard error	Standardized regression coefficient	F value	p value
HbA1c	0.096	0.010	0.213	93.390	<0.0001
SBP	0.004	0.001	0.165	57.398	<0.0001
Log-TG	0.136	0.032	0.096	18.102	<0.0001
Age	0.003	0.001	0.067	14.195	0.0002
Log-eVFA	0.144	0.044	0.078	10.839	0.0010

Adjusted r^2: 0.155.
Not accepted variables (F value <4.0) were log-adiponectin. TC, HDL-C and UA.

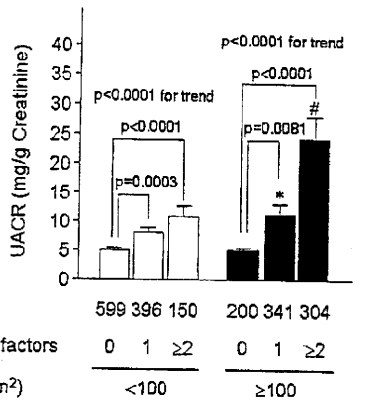

Fig. 2. Relationship between UACR, obesity-related risk factor accumulation and visceral fat accumulation. Obesity-related risk factors included hypertension, dyslipidemia, and hyperglycemia as described in Subjects and Methods section. Data are mean ± SEM. *; $p = 0.0874$ versus subjects with number of risk factor 1 plus eVFA <100 cm^2. #; $p < 0.05$ versus subjects with number of risk factor ≥2 plus eVFA <100 cm^2.

have greatly influenced urinary albumin excretion. These results indicate that body fat distribution, rather than with the degree of obesity, seems to be associated with UACR.

Next, we investigated the relationship between UACR, visceral fat accumulation and numbers of risk factors (Fig. 2). In both subjects with and without visceral fat accumulation, UACR increased significantly with increased numbers of risk factors. Subjects with one and two more risk factors, which were associated with accumulated visceral fat (≥100 cm^2), had higher UACR than those without visceral fat accumulation (<100 cm^2) (Fig. 2).

4. Discussion

Our cross-sectional study demonstrated that body fat distribution, i.e., visceral fat accumulation, is associated with increased urinary excretion of albumin. Albuminuria is a complex disorder influenced by genetic and environmental factors [17]. It is also frequently accompanied by one or more of the MetS parameters [5], including obesity [18], insulin resistance [19], diabetes [20], hypertension [21] and smoking [22]. Our results showed the relationship between UACR and these parameters (Tables 1 and 2). According to the MetS criteria proposed by the World Health Organization (WHO), albuminuria is stated as a metabolic disorder related to the MetS [23]. In the present study, subjects with MetS had significantly higher UACR than those without MetS, based on the modified Japanese criteria for MetS that include fasting and postprandial tests (Supplementary Fig. 1A), and based on the current Japanese criteria of the MetS (Supplementary Fig. 1B).

Nielsen and Jensen [24] reported that urinary albumin excretion did not correlate with visceral fat area in normotensive glucose-tolerant adults. However, several other groups showed that urinary albumin excretion correlated significantly with the waist–hip ratio [25] and WC [26]. Thus, there seems to be a controversy regarding the relationship between visceral fat and urinary albumin. It is also not clear whether visceral fat accumulation alone or the presence of risk factors, such as hypertension, hyperglycemia or dyslipidemia, explains the increase in urinary albumin excretion. The present study demonstrated that UACR levels correlated significantly with BMI, WC and visceral fat accumulation (Table 2). Moreover, stepwise multiple regression analysis showed that eVFA as well as HbA1c, SBP, TG and age were significant determinants of UACR (Table 3). Moreover, subjects with visceral fat accumulation had significantly higher UACR than those without visceral fat accumulation, both in those with and without overall obesity (Fig. 1). These results suggest that visceral fat accumulation *per se* could be associated with the increase in urinary albumin, independent of risk factor accumulation. Our results also demonstrated augmentation of UACR in the presence of multiple risk factors (Fig. 2). Therefore, a decrease in the number of risk factors by reduction of visceral fat should be beneficial in reducing urinary albumin excretion and probably prevention of cardiovascular diseases.

We measured adiponectin in blood to clarify the molecule mechanism in the relationship between visceral fat accumulation and microalbuminuria. The relationship between albuminuria and hypoadiponectinemia in obese subjects was suggested previously [27,28]. It is known that obesity and MetS cause renal dysfunction including albuminuria [29]. The underlying mechanisms are thought to include hyperinsulinemia, insulin resistance, increased vascular tone, endothelial dysfunction, renal sodium retention, increased rennin-angiotensin system and chronic inflammation through the dysregulation of adipocytokines [29]. We reported previously exacerbation of albuminuria and renal fibrosis through inflammation and oxidative stress in subtotal renal ablation model of adiponectin-knockout mice [30]. Another group also reported that adiponectin plays a protective role to reduce albuminuria by directly affecting podocyte function via 5′-AMP activated protein kinase (AMPK) pathway [27,31]. The present results demonstrated a negative correlation between albuminuria and serum adiponectin concentrations but the latter was not an independent factor, suggesting that accumulated visceral fat might produce more oxidative stress and that such increased oxidative stress causes dysregulated production of adipocytokines, e.g., low serum adiponectin levels [32] and that might cause increased urinary albumin.

Microalbuminuria is a significant risk factor for cardiovascular diseases [3]. In addition, albuminuria is reported to be an independent risk factor for cardiovascular morbidity and mortality [33]. Until some years ago, microalbuminuria was believed to be progressive and irreversible [34]. However, animal studies have demonstrated that regression of existing renal morphologic lesions is possible [35]. Reducing albuminuria is therefore considered to be an important therapeutic objective and may be a biomeasure of therapeutic success in type 2 diabetic patients [36]. Therefore, we should consider shifting the therapeutic focus from the prevention of progression to a reduction of albuminuria and, if a reduction of albuminuria cannot be achieved, encouraging more aggressive treatment. Further longitudinal studies are required to investigate whether albuminuria can be reversed by reduction of visceral fat. The relationship between reduction of visceral fat, reduction in albuminuria and reduction of cardiovascular events may be observed in patients with the MetS.

5. Conclusion

Our results demonstrated a positive correlation between visceral fat accumulation and urinary albumin excretion in middle-aged Japanese men. Evaluation of both visceral fat accumulation and urinary albumin may be important for preventing atherosclerotic diseases.

Limitations of the study

Our study has several limitations. First, the results may not be valid in females or non-Japanese populations. Second, although we used BIA to evaluate VFA in the present study, research on both visceral and subcutaneous fat area measured by computed tomography scan is needed to clarify the effects of visceral and subcutaneous adiposity. Third, UACR was calculated from a single spot urine specimen collected anytime between morning and afternoon. Multiple measurements on a like-for-like basis should

be preformed for a better assessment of the UACR. Fourth, we could not examine the relationship between UACR and smoking accurately, because we had no detail information of smoking amount in ex-smokers.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2010.02.037.

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Original Article

Association Between Stroke and Metabolic Syndrome in a Japanese Population: Jichi Medical School (JMS) Cohort Study

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ABSTRACT

Background: Metabolic syndrome increases the morbidity and mortality of cardiovascular diseases. However, few studies have examined the association between the incidence of stroke and metabolic syndrome, as defined by Japanese criteria. The aim of this study was to identify the association between stroke and metabolic syndrome, as defined by criteria used in Japan.

Methods: A total of 2205 subjects (920 men and 1285 women) were examined between 1992 and 1995 as part of the Jichi Medical School Cohort Study. Metabolic syndrome was defined using the Japanese criteria. Medical records, computed tomography, and magnetic resonance imaging were used to diagnose stroke. The Cox proportional-hazards model was used to analyze the association between metabolic syndrome and incident stroke.

Results: The prevalence of metabolic syndrome at baseline was 9.0% in men and 1.7% in women. There were 96 incident strokes during an 11.2-year follow-up period, 14 of which occurred in subjects with metabolic syndrome. Among subjects with metabolic syndrome, the age-adjusted hazard ratio (95% confidence interval) for stroke was 1.93 (0.94–3.96) in men and 6.85 (2.68–17.47) in women. After adjusting for age, smoking status, and alcohol drinking status, the hazard ratio was 1.89 (0.88–4.08) in men and 7.24 (2.82–18.58) in women. Age-adjusted hazard ratios associated with having 2 or more components of metabolic syndrome, with and without central obesity, were 2.93 (1.21–7.08) and 3.20 (1.23–8.31) in men and 1.75 (0.69–4.44) and 8.64 (2.82–28.03) in women, respectively.

Conclusions: The presence of metabolic syndrome, as defined by Japanese criteria, increases the risk of stroke; this effect was highly significant among women.

Key words: metabolic syndrome X; stroke; cohort studies; incidence; cardiovascular diseases

INTRODUCTION

Metabolic syndrome is defined as a cluster of risk factors—central obesity, hypertension, hyperlipidemia, and impaired glucose tolerance—that increases cardiovascular disease morbidity and mortality.[1,2] The third revision of the US Adult Treatment Panel guidelines for cholesterol testing and management was published by the National Cholesterol Education Program in 2001.[3] In 2005, the Examination Committee of Criteria for Metabolic Syndrome in Japan proposed a new set of criteria for the diagnosis of metabolic syndrome.[4] In the same year, the International Diabetes Federation presented a new criterion that became an essential component—race- and ethnic-specific measurement of waist circumference.[5] This parameter was modified to establish a Japanese set point for waist circumference in 2007.[6] In addition, the American Heart Association/National Heart, Lung, and Blood Institute modified the National Cholesterol Education Program criteria.[7]

In Japan, Health Checkups and Healthcare Advice with a Particular Focus on the Metabolic Syndrome were first implemented in April 2008.[8] The aims of this program are to prevent middle-aged men and women from developing chronic diseases, thereby reducing medical costs for individuals and the health care system. There is an urgent need for evidence from studies of the Japanese general population regarding the effects of metabolic syndrome, as defined by the Japanese criteria.

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Several studies have used various criteria to investigate the prevalence of metabolic syndrome in the Japanese general population; however, few have examined the association between metabolic syndrome, as defined by Japanese criteria, and stroke incidence.[9–11] In a previous report, our study group observed no significant association between all-cause mortality and metabolic syndrome, defined by Japanese criteria.[12]

The purpose of the present study was to examine the association between incident stroke and metabolic syndrome, as defined by Japanese criteria, among the Japanese general population.

METHODS

The Jichi Medical School (JMS) Cohort Study is a prospective population-based study that aims to clarify the risk factors of cardiovascular disease in a Japanese rural population. Details on the JMS Cohort Study design and some descriptive data were published previously.[13,14] Baseline data were collected between 1992 and 1995 in 12 rural communities. A total of 12 490 subjects (4911 men and 7579 women) participated in the 12 districts and the waist circumferences of 2286 subjects in 3 of these districts (Takasu, Wara, and Sakuma) were measured. From these 2286 subjects, we excluded 40 subjects who had a previous history of stroke or coronary heart disease, 40 from whom a blood sample could not be obtained, and 1 who was lost to follow-up. Ultimately, 2205 subjects (920 men and 1285 women) were available for observation in the present study. The participation rate for people invited to the mass screening examination was 56%.[15]

Mass screening examinations for cardiovascular disease have been conducted in Japan since 1983, in accordance with the Health and Medical Service Law for the Aged, and the same system was used to collect the present data. In each community, the local government office mailed a personal invitation to all subjects who were enrolled in this study. Trained interviewers used a standardized questionnaire to obtain information about their medical history and lifestyle. Smoking status was classified as current smoker, ex-smoker, or never-smoker; while alcohol drinking was classified as current drinker, ex-drinker, or never-drinker.

Body mass index was calculated as weight (kg) divided by the square of body height (m). Waist circumference was measured at the highest point of the iliac crest. Systolic and diastolic blood pressures were measured with a fully automated sphygmomanometer, the BP203RV-II (Nippon Colin, Komaki, Japan). All blood samples were collected after fasting for at least 8 hours. Serum total cholesterol and triglyceride levels were measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.5% for total cholesterol, and 1.7% for triglyceride). High-density lipoprotein cholesterol was measured by phosphotungstate precipitation (using an instrument by Wako, Osaka, Japan; interassay CV: 1.9%). Fasting plasma glucose was measured enzymatically (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%).

The subjects who were enrolled in this study were followed-up and their cardiovascular events were investigated and recorded. If they were hospitalized for any reason, their medical records, including duplicate computed tomography scans and magnetic resonance imaging, were checked for evidence of stroke. Each municipal government annually obtained information about subjects who had relocated out of the area. Death certificates were collected from public health centers until the end of 2005, with official permission from the Agency of General Affairs and the Ministry of Health, Labour and Welfare.

The criteria for stroke were sudden onset of a focal and nonconvulsive neurological deficit that persisted for longer than 24 hours; stroke subtype was determined according to the criteria of the National Institute of Neurological Disorders and Stroke.[16] In this study, cerebral infarction and cerebral hemorrhage were defined as stroke, but cases of subarachnoid hemorrhage were not. All probable cases of stroke in this study were evaluated independently by a diagnosis committee composed of a radiologist and a neurologist, with the aid of computed tomography and magnetic resonance imaging.[13]

Written informed consent for participation in the study was obtained from each responder at the mass screening health checkup. We explained that data would be gathered by using the questionnaire and blood samples, that participants' health status would be checked, and that their hospital medical records would be examined if a stroke was suspected. All responders agreed to join the study. The Institutional Review Board of Jichi Medical School for Ethical Issues approved this study.

Metabolic syndrome

The original diagnostic definition of metabolic syndrome in Japan was promulgated by the Examination Committee of Criteria for Metabolic Syndrome in April 2005.[4] For the purposes of this study, metabolic syndrome was defined as a waist circumference of at least 85 cm in men or 90 cm in women, plus at least 2 of the following: (1) triglycerides ≥1.7 mmol/L (150 mg/dL) or high-density lipoprotein cholesterol <1.0 mmol/L (40 mg/dL), (2) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and (3) fasting plasma glucose ≥6.1 mmol/L (110 mg/dL). Subjects who were being treated for diabetes and hypertension were identified by questionnaire at baseline and were included in the study; however, treatment for hyperlipidemia was not taken into account because the questionnaire was not equipped to differentiate those treated for elevated total cholesterol, triglyceride, and lower high-density lipoprotein cholesterol.

Table 1. Clinical characteristics of subjects with and without metabolic syndrome

	Without metabolic syndrome	With metabolic syndrome	*P*-value[a]
Males			
n (%)	837 (91.0)	83 (9.0)	
Age (year)	56.3 ± 12.4	57.9 ± 12.1	N.S.
BMI (kg/m^2)	22.4 ± 2.6	26.4 ± 2.1	<0.001
Waist circumference (cm)	77.9 ± 7.8	90.2 ± 4.6	<0.001
Systolic blood pressure (mm Hg)	127.4 ± 21.2	143.1 ± 17.9	<0.001
Diastolic blood pressure (mm Hg)	76.8 ± 12.2	86.1 ± 11.2	<0.001
Fasting plasma glucose (mmol/L)	5.3 ± 0.9	6.0 ± 1.5	<0.001
Total cholesterol (mmol/L)	4.8 ± 0.9	5.0 ± 0.8	0.01
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.0 ± 0.2	<0.001
Triglyceride (mmol/L)	1.3 ± 1.0	2.2 ± 1.2	<0.001
Current smoking, *n* (%)	404 (49.4)	36 (43.9)	N.S.
Current alcohol drinking, *n* (%)	636 (77.8)	61 (74.4)	N.S.
Diabetes mellitus, *n* (%)	66 (7.9)	32 (38.6)	<0.001
Hypertension, *n* (%)	352 (42.1)	76 (91.6)	<0.001
Females			
n (%)	1263 (98.3)	22 (1.7)	
Age (year)	55.9 ± 12.1	62.0 ± 10.7	0.01
BMI (kg/m^2)	22.9 ± 3.0	28.9 ± 4.5	<0.001
Waist circumference (cm)	73.6 ± 8.7	93.4 ± 3.7	<0.001
Systolic blood pressure (mm Hg)	130.8 ± 22.5	151.0 ± 19.5	<0.001
Diastolic blood pressure (mm Hg)	76.9 ± 13.1	86.4 ± 9.5	<0.001
Fasting plasma glucose (mmol/L)	5.1 ± 0.9	6.3 ± 2.0	<0.01
Total cholesterol (mmol/L)	5.1 ± 0.9	5.5 ± 0.8	0.02
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.1 ± 0.2	<0.001
Triglyceride (mmol/L)	1.1 ± 0.6	2.0 ± 0.9	<0.001
Current smoking, *n* (%)	56 (4.5)	1 (4.5)	N.S.
Current alcohol drinking, *n* (%)	411 (33.1)	7 (31.8)	N.S.
Diabetes mellitus, *n* (%)	80 (6.3)	8 (36.4)	<0.001
Hypertension, *n* (%)	613 (48.5)	21 (95.5)	<0.001

BMI: body mass index.
HDL cholesterol: high-density lipoprotein cholesterol.
N.S.: not significant.
[a]*P*-values were calculated using the *t*-test for variables and the chi-square test for rates.
Data are expressed as the mean ± standard deviation (SD) for variables and as a percentage for rates.

Statistical analysis

All statistical analyses were performed on a personal computer with the Statistical Package for Social Science® (SPSS) for Windows (SPSS Japan Inc., version 11.5, Tokyo, Japan). The results are expressed as the mean ± standard deviation (SD). *P* values were calculated using the *t*-test for variables. Smoking status, alcohol-drinking status, and histories of hypertension and diabetes mellitus were tested using the chi-square test.

The Cox proportional-hazards model was used to calculate the hazard ratios (HRs) for stroke incidence after adjustment for age, smoking status, and alcohol-drinking status, with or without metabolic syndrome, using the Japanese criteria. The crude stroke incidence was calculated per 1000 person-years. A *P* value <0.05 was considered significant.

RESULTS

The total number of person-years of observation was 24 653, the mean follow-up period (± SD) was 11.2 ± 2.4 years, and the mean age at baseline ± SD was 56.2 ± 12.2 (56.5 ± 12.4 in men and 56.0 ± 12.1 in women). There were 96 incident strokes during the observation period: 54 (5.9%) in men and 42 (3.3%) in women.

Table 1 shows the characteristics of subjects with and without metabolic syndrome (stratified by sex). At baseline, the prevalence of metabolic syndrome, as per the Japanese definition, was 9.0% in men and 1.7% in women. There were no significant differences in smoking or alcohol drinking status between the subjects with and without metabolic syndrome in either sex. The women with metabolic syndrome were older than the women without metabolic syndrome; however, among men, there was no such age difference. With the exception of high-density lipoprotein cholesterol, the values for other parameters were significantly higher in subjects with, as compared to without, metabolic syndrome.

Table 2 shows the crude stroke incidence rate and HRs for metabolic syndrome, calculated by the Cox proportional-hazards model, with the absence of metabolic syndrome as reference. There were 96 incident strokes (in 54 men and

Table 2. Adjusted hazard ratios in men and women with and without metabolic syndrome

	Males		Females	
	Without metabolic syndrome	With metabolic syndrome	Without metabolic syndrome	With metabolic syndrome
All subjects, *n*	920		1285	
Subjects with metabolic syndrome, *n* (%)	837 (91.0)	83 (9.0)	1263 (98.3)	22 (1.7)
Stroke incidence, *n*	45	9	37	5
Crude incidence rate[a]	4.9	10.3	2.6	22.0
HR - model 1[b] (95% CI)	reference	1.93 (0.94–3.96)	reference	6.85 (2.68–17.47)
HR - model 2[c] (95% CI)	reference	1.89 (0.88–4.08)	reference	7.24 (2.82–18.58)

Metabolic syndrome was defined using Japanese criteria.
HR: hazard ratio.
CI: confidence interval.
[a]per 1000 person-years.
[b]Hazard ratio adjusted for age.
[c]Hazard ratio adjusted for age, smoking status, and alcohol drinking status.

Table 3. Hazard ratios for stroke, by number of supplementary components of metabolic syndrome, presence of central obesity, and sex

No. of supplementary components	*n*	No. of strokes	Crude incidence rate[a]	Model 1[b]		Model 2[c]	
				HR	(95% CI)	HR	(95% CI)
Males							
Central obesity (−)	685						
0	259	8	2.8	1.00	reference	1.00	reference
1	298	20	6.2	1.81	(0.79–4.14)	1.73	(0.75–3.97)
≥2	128	13	9.8	2.93	(1.21–7.08)	2.53	(1.02–6.24)
Central obesity (+)	235						
0	36	0	0	—	—	—	—
1	116	4	3.0	1.24	(0.37–4.12)	0.91	(0.24–3.42)
≥2	83	9	10.3	3.20	(1.23–8.31)	2.83	(1.05–7.59)
Females							
Central obesity (−)	1213						
0	510	8	1.4	1.00	reference	1.00	reference
1	503	19	3.3	1.31	(0.57–3.01)	1.31	(0.59–3.10)
≥2	200	10	4.4	1.75	(0.69–4.44)	1.83	(0.72–4.68)
Central obesity (+)	72						
0	14	0	0	—	—	—	—
1	36	0	0	—	—	—	—
≥2	22	5	22.0	8.64	(2.82–26.51)	9.09	(2.95–28.03)

HR: hazard ratio.
CI: confidence interval.
Central obesity: waist circumference ≥85 cm in males or ≥90 cm in females.
[a]per 1000 person-years.
[b]Hazard ratio adjusted for age.
[c]Hazard ratio adjusted for age, smoking status, and alcohol drinking status.

42 women) during the follow-up period. The age-adjusted HRs (95% confidence intervals [CI]) were 1.93 (0.94–3.96) in men and 6.85 (2.68–17.47) in women. After further adjustment for current smoking and alcohol drinking statuses, the HRs were 1.89 (0.88–4.08) for men and 7.24 (2.82–18.58) for women.

Next, we classified all subjects into 6 groups by the presence of 0, 1, and 2 or more supplementary components of metabolic syndrome, in men and women with and without central obesity (Tables 3 and 4). Table 3 shows the crude stroke incidence rates and HRs calculated by using the Cox proportional-hazards model. Subjects are classified by the number of supplementary components of metabolic syndrome, the presence of central obesity, and by sex. After adjustment for age and further adjustment for current smoking and alcoholic statuses, the HRs increased in both men and women with 2 or more supplementary components of metabolic syndrome, regardless of central obesity; however, in women, HRs markedly increased in those with central obesity and 2 or more supplementary components of metabolic syndrome, as compared to women without central obesity. There were no strokes among men with central

Table 4. Hazard ratios of stroke incidence with metabolic components with or without central obesity (using various cut-off value of waist circumference) by sex

No. of supplementary components	WC ≥80 cm					WC ≥85 cm					WC ≥90 cm				
	No. of strokes/total	Model 1[a]		Model 2[b]		No. of strokes/total	Model 1[a]		Model 2[b]		No. of strokes/total	Model 1[a]		Model 2[b]	
		HR	(95% CI)	HR	(95% CI)		HR	(95% CI)	HR	(95% CI)		HR	(95% CI)	HR	(95% CI)
Males															
Central obesity (−)															
0	5/208	1.00	Reference	1.00	Reference	8/259	1.00	Reference	1.00	Reference	8/280	1.00	Reference	1.00	Reference
1	17/215	2.58	(0.94–7.04)	2.52	(0.92–6.91)	20/298	1.81	(0.79–4.14)	1.73	(0.75–3.97)	23/374	1.83	(0.81–4.10)	1.75	(0.78–3.95)
≥2	9/80	3.76	(1.26–11.27)	3.24	(1.05–9.98)	13/128	2.93	(1.21–7.08)	2.53	(1.02–6.24)	17/169	2.99	(1.28–6.95)	2.50	(1.05–5.95)
Central obesity (+)															
0	3/87	1.88	(0.45–7.88)	2.08	(0.49–8.73)	0/36	—	—	—	—	0/15	—	—	—	—
1	7/199	1.65	(0.52–5.20)	1.41	(0.43–4.63)	4/116	1.24	(0.37–4.12)	0.91	(0.24–3.24)	1/40	0.98	(0.12–7.85)	—	—
≥2	13/131	4.17	(1.48–11.70)	3.83	(1.34–10.92)	9/83	3.20	(1.23–8.31)	2.83	(1.05–7.59)	5/42	4.10	(1.34–12.53)	4.05	(1.32–12.44)
Females															
Central obesity (−)															
0	8/437	1.00	Reference	1.00	Reference	8/481	1.00	Reference	1.00	Reference	8/510	1.00	Reference	1.00	Reference
1	16/388	1.32	(0.56–3.09)	1.27	(0.54–3.00)	17/455	1.31	(0.56–3.05)	1.26	(0.54–2.94)	19/503	1.35	(0.59–3.10)	1.31	(0.57–3.01)
≥2	8/127	1.83	(0.69–4.89)	1.96	(0.73–5.27)	9/171	1.76	(0.68–4.58)	1.84	(0.71–4.79)	10/200	1.75	(0.69–4.44)	1.83	(0.72–4.64)
Central obesity (+)															
0	0/87	—	—	—	—	0/43	—	—	—	—	0/14	—	—	—	—
1	3/151	0.52	(0.14–1.96)	0.53	(0.14–2.12)	2/82	0.62	(0.13–2.95)	0.70	(0.15–3.34)	0/36	—	—	—	—
≥2	7/95	2.30	(0.88–6.38)	2.42	(0.87–6.72)	6/51	3.83	(1.33–11.07)	4.38	(1.51–12.75)	5/22	8.64	(2.82–26.51)	9.09	(2.95–28.03)

HR: hazard ratio.
CI: confidence interval.
WC: Waist circumference.
[a]Hazard ratios adjusted for age.
[b]Hazard ratio adjusted for age, smoking status, and alcohol drinking status.

obesity but no supplementary components of metabolic syndrome. There were also no strokes among women with central obesity and fewer than 2 supplementary components of metabolic syndrome.

Table 4 shows HRs calculated using the Cox proportional-hazards model for stroke incidence with 0, 1, and 2 or more supplementary components of metabolic syndrome, in men and women with and without central obesity, using subjects with no supplementary components of metabolic syndrome as a reference. The HRs for stroke were calculated for both sexes using different cutoffs for waist circumference (80, 85, and 90 cm) and the number of supplementary components of metabolic syndrome, as defined by the Japanese criteria. The HRs for stroke among subjects with 2 or more supplementary components of metabolic syndrome were higher in subjects with, as compared to without, central obesity, when the cutoffs for waist circumferences were 90 cm in men and 85 cm in women.

DISCUSSION

We investigated the associations between stroke and metabolic syndrome, as defined by Japanese criteria, in the general Japanese population. Our findings suggest that metabolic syndrome was associated with an increased incidence of stroke; this effect was statistically significant in women.

Several studies have examined the association between stroke incidence and metabolic syndrome in Japan.[9–11,17,18] In the Hisayama Study, metabolic syndrome, as defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria, was associated with increased morbidity for cardiovascular diseases, including stroke.[18] In the NIPPON DATA 80, metabolic syndrome, as defined by the modified National Cholesterol Education Program Adult Treatment Panel III using body mass index instead of waist circumference, was associated with higher incidences of ischemic stroke and ischemic heart disease.[17] However, few such studies have used the Japanese definition of metabolic syndrome.[9–11] Saito et al reported that the overall prevalence of metabolic syndrome, as defined by the Japanese criteria, was 6.4%, that the sex- and age-adjusted HR for stroke was 0.82, and that metabolic syndrome was not associated with stroke.[9] They suggested that the Japanese criteria for metabolic syndrome should include 1 requisite component—waist circumference. The use of such a definition weakens the effects of atherosclerotic risk factors (eg, glucose intolerance, hypertension, and dyslipidemia). Takahashi et al reported that the prevalence of metabolic syndrome, defined by the Japanese criteria, was 11.0% in men and 1.1% in women, and that the HR adjusted for age and smoking status was 23.1 in women. They suggested that metabolic syndrome, as defined by the Japanese criteria, was associated with stroke in women but not in men.[10] Our findings were consistent with theirs; however, their study had a smaller sample size and wider 95% CIs for the HRs.

In the Suita Study, the frequencies of metabolic syndrome in men and women, based on the Japanese criteria, were 17.7% and 5.0%, and the age-adjusted HRs were 1.21 and 2.09; after further adjustment for current smoking and alcohol drinking status, the HRs were 1.27 and 2.05.[11] In addition, they noted that metabolic syndrome, defined by Japanese criteria, was associated with cardiovascular disease, myocardial infarction, and all-stroke incidence only in women. The investigators suggested that the number of metabolic components might be more strongly associated with cardiovascular disease incidence than the requisite waist circumference criterion. They observed elevated HRs in both sexes, as was the case in the present study; however, they observed a statistically significant association between metabolic syndrome and stroke only in women.

Table 3 shows that, in men, the HRs for stroke incidence in men with 2 or more supplementary components of metabolic syndrome were similar in men with and without central obesity; however, among women, the HRs in women with 2 or more supplementary components of metabolic syndrome and central obesity had a higher risk of stroke than did those without central obesity. The prevalence of central obesity, which is included in the Japanese diagnostic criteria for metabolic syndrome, was 25.5% in men and 5.6% in women. As compared with other populations, the proportion of women with metabolic syndrome was not low.[12] However, the 95% CIs of the HRs are likely to be wider for women because of the low prevalence of metabolic syndrome.

Some have reported that waist circumference is positively associated with the risk of cardiovascular events.[19,20] In our study, there were no strokes either among men with central obesity and no supplementary components of metabolic syndrome or among women with central obesity and 0 or 1 supplementary component of metabolic syndrome (Table 3). Different waist circumference cutoffs (80, 85, and 90 cm) were used to divide the subjects into 6 groups (Table 4). When the waist circumference cutoff was 90 cm for men and 85 cm for women, the HRs for stroke were higher among subjects with central obesity and 2 or more supplementary components of metabolic syndrome than those for subjects without central obesity. Consequently, we believe that the appropriate cutoffs for waist circumference in the Japanese criteria for metabolic syndrome are 90 cm in men and 85 cm in women; moreover, our findings indicate that, in addition to increased waist circumference, the combination of central obesity and 2 or more supplementary components of metabolic syndrome is associated with a higher risk for stroke.

Waist circumference is a requisite in the diagnostic definitions of both the Japanese and International Diabetes Federations; however, the World Health Organization and National Cholesterol Education Program Adult Treatment Panel III criteria include waist circumference as only one of

several components. The Japan Diabetes Complication Study (JDCS) observed that there was an association between metabolic syndrome and stroke when the World Health Organization or National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria were used[21]; however, in the same patient group (ie, those observed in the JDCS), there was no significant association with stroke when the diagnostic criteria advanced by the International Diabetes Federation were used.[22] Their results show that different diagnostic definitions of metabolic syndrome can lead to substantially different assessments of the risks for cardiovascular events in the same population.

In the present study, using waist circumference cutoffs of 90 cm in men and 80 cm in women, which the International Diabetes Federation recommend for Japanese, we re-examined the association between stroke and metabolic syndrome (Table 4). The HRs for stroke increased in both sexes; however, the results were significant only when men with no supplementary components of metabolic syndrome were used as the reference.

The strengths of this study are: (1) it was a longitudinal population-based study, (2) there was almost complete follow-up of subjects who developed cardiovascular disease (including stroke), (3) the follow-up period was long, and (4) fasting blood samples were collected.

The most notable limitation of this study is its small sample size. Because of this, the 95% CIs for the HRs are relatively wide; however, the study is valuable because few longitudinal studies have investigated metabolic syndrome in the Japanese general population. We believe that a longer period of follow-up will solve the problem of small sample size.

Other limitations include: (1) waist circumference was measured at the highest level of the iliac crest; (2) the subjects resided in only 3 rural districts; and (3) drug therapy for dyslipidemia was not identified on the questionnaire. Measurement of waist circumference was not common at health examinations between 1992 and 1995, when the baseline data for the general population were obtained. Even at present, various methods are used to measure waist circumference. According to the Japanese criteria, it should be measured at the level of the umbilicus while the subject is standing and breathing normally. We measured it using the method that is utilized to obtain the waist-to-hip ratio, which is endorsed by the World Health Organization.[23] However, the use of this method may have underestimated waist circumference.

In conclusion, metabolic syndrome, as defined by the original Japanese criteria, was positively associated with stroke. Furthermore, in women, there was a statistically significant difference in stroke incidence between women with and without metabolic syndrome. We hope that there will be larger and more comprehensive prospective studies of cardiovascular morbidity and mortality in the Japanese general population.

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Original Article

Risk Charts Illustrating the 10-year Risk of Myocardial Infarction among Residents of Japanese Rural Communities: The JMS Cohort Study

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ABSTRACT

Background: Risk charts that depict the absolute risk of myocardial infarction (MI) for each combination of risk factors in individuals are convenient and beneficial tools for primary prevention of ischemic heart disease. Although risk charts have been developed using data from North American and European cardiovascular cohort studies, there is no such chart derived from cardiovascular incidence data obtained from the Japanese population.

Methods and Results: We calculated and constructed risk charts that estimate the 10-year absolute risk of MI by using data from the Jichi Medical School (JMS) Cohort Study—a prospective cohort study which followed 12490 participants in 12 Japanese rural communities for an average of 10.9 years. We identified 92 cases of a clinically-certified MI event. Color-coded risk charts were created by calculating the absolute risk associated with the following conventional cardiovascular risk factors: age, sex, smoking status, diabetes status, systolic blood pressure, and serum total cholesterol.

Conclusions: In health education and clinical practice, particularly in rural communities, these charts should prove useful in understanding the risks of MI, without the need for cumbersome calculations. In addition, they can be expected to provide benefits by improving existing risk factors in individuals.

Key words: myocardial infarction; blood pressure; cholesterol; smoking; diabetes; cohort study

INTRODUCTION

Ischemic heart disease is the leading cause of death in most Western countries.[1] In Japan, although mortality from ischemic heart disease is much lower than that in Western countries, it is still a major cause of death.[1,2] Risk factors known to have an impact on ischemic heart disease include age, sex, blood pressure, smoking, lipid profile, and diabetes.[3] Recently, population groups with increased coronary risks, including individuals with hyperlipidemia and those with diabetes, have been growing rapidly in Japan. Thus, there is the potential for a commensurate increase in the incidence of ischemic heart disease in the near future. However, some cardiovascular cohort studies conducted in Japan have indicated that the incidence of coronary heart disease has remained steady for the last several decades, and that mortality has slightly decreased.[2,4,5] It is hypothesized that this trend is due to recent improvements in treatment measures for coronary heart disease, and to improved risk factor management, including pervasive hypertension control and a decrease in the rate of tobacco use.[3]

For each individual with one or more risk factors, it is beneficial to know the probability of coronary heart disease. This information would enable the individual to appreciate the necessity of medical intervention and self-management of risk factors. For this purpose, several methods for calculating the absolute risk of coronary heart disease have been developed using data from large-scale cohort studies.[6,7] Calculations using complicated mathematical formulae are cumbersome, however, and therefore not suitable for health education in communities and clinics. Risk charts that clearly illustrate the absolute risk of coronary heart disease for each combination

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of risk factors allow for improved public understanding and participation. Such charts have been developed using data from the Framingham study in the United States, the SCORE project in Europe, and the NIPPON DATA80 study in Japan, and are now available for use.[8–10]

However, there are problems if Japanese clinicians and healthcare workers attempt to utilize existing risk charts that are based on data from cohort studies in the United States and Europe. First, the incidences of coronary heart disease in these countries substantially differ from that observed in Japan. In a comparison of the results from the Framingham study with data obtained from a community-based cohort study in Japan, the white middle class population in the United States has a 5 to 6 times higher incidence of myocardial infarction (MI).[5,11,12] Applying the Framingham-based risk chart to a Japanese population thus considerably overestimates the risk of coronary heart disease. Second, there may be differences in the degree of impact of each risk factor on coronary heart disease among different racial and cultural groups. To cite one example, diabetes and hypercholesterolemia are strong contributing factors to MI in white American populations, but they were not identified as risk factors for MI in some Japanese cohort studies.[4,5,11,13–15]

Current risk charts based on Japanese cohort studies are therefore needed. Charts developed using data from NIPPON DATA80 are now available in Japan. Although these charts were the first to use data from a Japanese population to assess cardiovascular risk, they are based on mortality data and the outcome measure was coronary death, not coronary incidence.[16,17] These mortality data did not include non-fatal coronary events. Moreover, diagnoses in the NIPPON DATA80 were based on data from death certificates, and the accuracy of a diagnosis in such circumstances is always a concern . In order to estimate accurately an individual's risk of coronary heart disease, risk charts based on incidence data from the Japanese population are needed.

The Jichi Medical School (JMS) Cohort Study is a multi-community prospective study that follows rural residents in Japan and monitors cardiovascular disease events.[18–20] In this article we utilize data from the JMS Cohort Study to develop risk assessment charts for MI.

METHODS

Study population

The JMS Cohort Study began in 1992. Its primary objective was to clarify the relations between potential risk factors and cardiovascular disease in 12 rural districts in Japan.[18] The baseline data of this cohort study were obtained between April 1992 and July 1995. If several sets of data were obtained for a single participant during that period, the first set was used as the baseline information. The baseline data were collected as part of a national mass-screening program. In Japan, mass screening for cardiovascular disease has been conducted since 1982, in accordance with the Health and Medical Service for the Aged Act of 1981. Local government offices in each community issued invitations to eligible residents for the mass screening, and personal invitations were also sent to all potential participants by mail. As a result, 12 490 participants were eligible (4913 males and 7577 females) in the adult age groups (19–93 years). The overall response rate among the 12 communities was 65.0%.

Among the possible 12 490 participants, 95 (0.8%) who did not sign the agreement to participate in the study, 7 (0.06%) who had no follow-up data, and 65 (0.5%) who had a past history of MI were excluded. The final study group eligible for analysis therefore comprised 12 323 participants (4829 men and 7494 women).

Measurement of baseline variables

To synchronize the methods of data collection, we established a central committee composed of the chief medical officers from all the participating districts. This committee developed a detailed written methodology for data collection. Systolic blood pressure and diastolic blood pressure were measured with a fully-automated sphygmomanometer, the BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of a seated participant who had rested in a sitting position for 5 minutes before measurement. Information about medical history and lifestyle was gathered by means of a written questionnaire.

Blood samples were drawn from the antecubital vein of seated participants, with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing a 1/10 volume of 3.8% trisodium citrate for blood glucose, and no additives for lipids. Tubes were centrifuged at 3000g for 15 minutes at room temperature. Serum samples were stored at 4 °C in refrigerated containers if the analysis was to be performed within a few days. Otherwise, the samples were frozen until analysis. Plasma samples were frozen as rapidly as possible to −80 °C for storage, until laboratory examination could be performed.

Total cholesterol was measured using a commercially available enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.5%). Blood glucose was measured via a commercially available enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%). In this study, blood samples from 5547 (45.0%) participants were collected after overnight fasting. Diabetic participants were defined as those with currently treated diabetes, plasma glucose ≥126 mg/dl after an overnight fast, or casual blood glucose ≥200 mg/dl. Participants were asked to indicate whether they were current smokers or not.

Follow-up

Repeat examinations (part of the national mass-screening program) were used to follow most participants every year. Those examined were asked whether they had experienced an

MI after enrolling. Participants who did not come to an appointed screening examination were contacted by mail or phone. Public health nurses visited the participants to obtain pertinent information when necessary. In this study 100% of the participants were contacted. Those with a history of MI were asked where (in which hospital) they had been treated, and the date of medical diagnosis. Medical records at hospitals in the study area were also consulted to determine if these participants had been treated. If an incident was suspected, pertinent electrocardiograms were obtained in accordance with the law for diagnostic identification of MI. The medical records of all the suspected cases were obtained during follow-up. Diagnoses were determined independently by a diagnosis committee composed of 1 radiologist, 1 neurologist, and 2 cardiologists. A diagnosis of MI was determined by using the criteria of the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, a multinational collaborative project to monitor coronary events from the mid-1980s to the mid-1990s.[21] Participants who met the MONICA criteria for a nonfatal or fatal "definite myocardial infarction" or "possible myocardial infarction" were defined as MI cases.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 11.5 (SPSS Inc, Japan). Data obtained for men and women were analyzed separately, and a Cox proportional hazards model was used to calculate the 10-year absolute risk of MI for each risk profile. Age, systolic blood pressure, total cholesterol, diabetes status, and current smoking status were entered into the proportional hazards model as explanatory variables. In the model, age, systolic blood pressure, and total cholesterol were treated as continuous variables, and diabetes status and smoking status were treated as dichotomous variables. The survival probability S(T:X) of a person with a risk X at time T was represented as $S(T:X) = ([S_0(T)]^{\exp(BX)})^{\exp(B(X-Xm))}$, where $S_0(T)$ is the survival probability corresponding to the standard hazard, B is the regression coefficient, and X_m is the population mean of risk X. The 10-year absolute risk of a person with risk X was thus defined as 1-S(10:X).[17] The 10-year absolute risk of a person with multiple risk factors was calculated in a similar manner. For example, where X, Y, and Z are the risk factors, $S(T:X,Y,Z) = [S_0(T)]^{\exp(BX*B(X-Xm)+BY*B(Y-Ym)+BZ*B(Z-Zm))}$. Risk charts were created for both sexes based on calculations of the absolute risk associated with a quintet of conventional cardiovascular risk factors: age, smoking status, diabetes status, systolic blood pressure, and serum total cholesterol. Age was grouped into 5 categories: under 40, 40–49, 50–59, 60–69, and 70 years or older. Systolic blood pressure was grouped into 5 categories: less than 120, 120–139, 140–159, 160–179, and 180 mm Hg or higher. Total cholesterol was grouped into 6 categories: less than 180, 180–199, 200–219, 220–239, 240–259, and 260 mg/dl or higher. The other risk factors were treated as dichotomous variables. In total, the charts show absolute risks for 1200 combinations of risk factors. The risk charts were color-coded so that users could easily estimate their probability of a future MI.

Ethical issues

The study design and procedures were approved by each community government, and by the Ethical Committee of Epidemiologic Research at Jichi Medical University. Written informed consent to participate in the study was obtained individually from each respondent to the mass screening.

RESULTS

The baseline characteristics of study participants are shown in Table 1. The mean follow-up period (± SD) was 10.9 ± 2.25 (10.8 ± 2.44 years in men and 11.0 ± 2.12 years in women). Because the cohort is based in rural communities, the participants were older (mean age 55.0 years old in men and 55.3 in women) and more were female (60.8%), as compared with the Japanese general population. Ninety-two cases (64 men and 28 women) of MI were identified during follow-up. The overall crude incidence rate was 1.23/1000 person-years in men and 0.34/1000 person-years in women. After adjustment for age by the direct method, the incidence rate was 0.83/1000 person-years in men and 0.31/1000 person-years in women.[22] The results of the proportional hazards analysis, upon which the absolute risk calculations were based, are shown in Table 2.

Figure 1 and Figure 2 show the color-coded 10-year absolute risk of MI for each combination of risk factors. Diabetes in men and current smoking status in women were not included in the risk estimations because these 2 factors were not significantly associated with MI incidence, as shown in Table 2. The charts were separated into 2 tables according to sex, and each was then subdivided further according to diabetes status and smoking status. Risk can be estimated by matching the person's age to the nearest age grouping, total

Table 1. Baseline characteristics of participants

	Men		Women	
Number of participants at baseline	4829	(100)	7494	(100.0)
Mean length of follow-up, years (SD)	10.8	(2.4)	11.0	(2.1)
Mean age at baseline, years (SD)	55.0	(12.0)	55.3	(11.3)
Mean body mass index, kg/m^2 (SD)	23.0	(2.9)	23.2	(3.2)
Current smokers	2248	(46.6)	380	(5.1)
Mean total cholesterol, mg/dl (SD)	184.9	(34.2)	196.7	(34.8)
Mean systolic blood pressure, mm Hg (SD)	131.4	(20.5)	128.2	(21.0)
With diabetes	249	(5.2)	198	(2.6)
Cumulative incidence of myocardial infarction	64	(1.3)	28	(0.4)

Data are expressed as number (%) unless otherwise indicated.
SD: standard deviation
Diabetes: those with currently treated diabetes, plasma glucose ≥126 mg/dl after an overnight fast, or casual blood glucose ≥200 mg/dl.

Table 2. Hazard ratio for myocardial infarction for each risk factor in men and women

Sex	Variable	HR	95% CI	P
Men	Age (1 yr)	1.087	1.056– 1.120	<0.001
	SBP (1 mm Hg)	1.016	1.004– 1.027	0.006
	T-chol (1 mg/dl)	1.013	1.005– 1.020	0.001
	Diabetes	0.791	0.245– 2.553	0.695
	Current smoking	2.657	1.524– 4.631	0.001
Women	Age (1 yr)	1.106	1.044– 1.171	0.001
	SBP (1 mm Hg)	1.023	1.004– 1.041	0.015
	T-chol (1 mg/dl)	1.009	0.996– 1.021	0.168
	Diabetes	4.372	1.454–13.150	0.009
	Current smoking	3.047	0.704–13.200	0.136

HR: Hazard ratio
95% CI: 95% confidence interval

cholesterol level to the corresponding range, and blood pressure to the nearest multiple of 20 mm Hg.

The risk of MI increased as systolic blood pressure rose, which is clearly indicated by the data shown in the Figures. Similarly, the risk of MI increased with elevation of total cholesterol level. Current smoking in men and diabetes in women also increased the 10-year risk of MI.

DISCUSSION

We developed simple risk charts by using data on a specific cardiovascular event (MI) from a Japanese cohort study. The charts illustrate the 10-year absolute risk of MI associated with sex, age, smoking status, diabetes status, total cholesterol, and

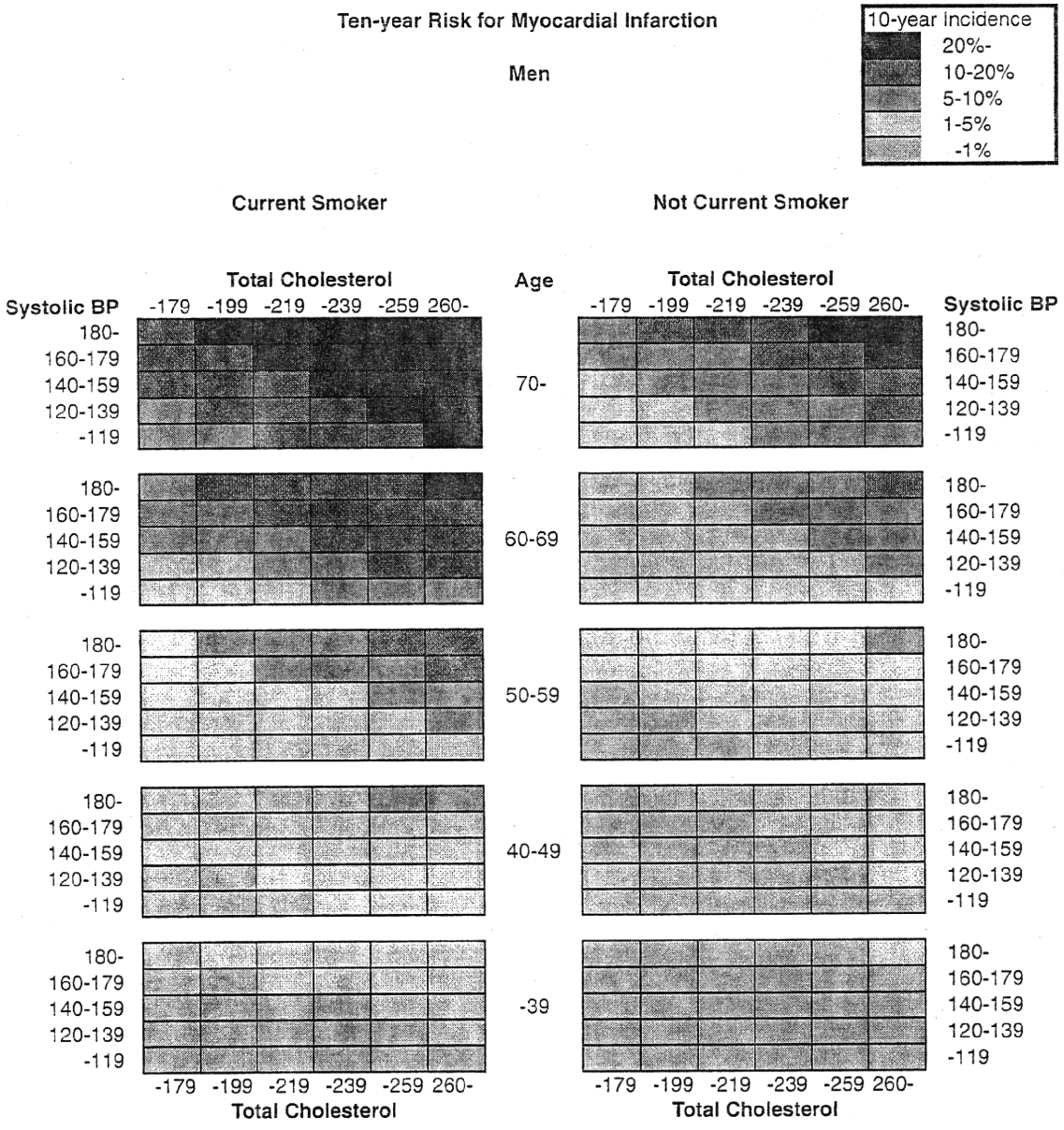

Figure 1. Chart showing 10-year risk for myocardial infarction in men