could change depending on the way of grouping the subjects or on the way of selecting the reference group. Given that this limitation might have overestimated the cut-off point, the true cut-off point for detection of high-risk subjects may be lower than 1 mg/L. A second limitation is that our findings are based on a 1-time measurement of serum hs-CRP, which may not accurately reflect the status of a study participant. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A third limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.[10] The last limitation is that our study lacked information on drug use at baseline and during the follow-up period. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.[33] However, these medications were rarely used in Japan in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings. It is also known that some medications have been shown to be beneficial for prevention of CHD, and high-risk individuals with higher hs-CRP levels were likely to receive these medications. Given that this limitation might have underestimated the association between hs-CRP and CHD, the true association may be stronger than that obtained from the present analysis.

In conclusion, the present analysis has clearly demonstrated that hs-CRP levels were associated with future coronary events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. High-risk approaches for the prevention of CHD using hs-CRP measurement are likely to provide additional protection against the burden of CHD in Japan.

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Disclosures

None.

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LDL Cholesterol and the Development of Stroke Subtypes and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Although the relation between serum LDL cholesterol level and coronary heart disease (CHD) is well established, its relation with stroke subtypes is less clear.

Methods—A total of 2351 inhabitants age ≥40 years in a Japanese community were followed up for 19 years.

Results—During follow-up, 271 subjects developed stroke and 144 developed CHD. Whereas the age- and sex-adjusted incidences of CHD significantly increased with increasing LDL cholesterol levels (P for trend <0.001), the associations between LDL cholesterol level and the incidences of ischemic or hemorrhagic stroke were not significant. The age- and sex-adjusted incidences of atherothrombotic infarctions (ATIs) and lacunar infarctions (LIs) significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATIs and=0.02 for LIs), but no such association was observed for cardioembolic infarction. After multivariate adjustment, the positive associations of LDL cholesterol level with the risks of ATI and CHD remained significant (P for trend=0.02 for ATIs and=0.03 for CHD), whereas the association with LIs was not significant. The risk of ATI significantly increased in the fourth quartile of LDL cholesterol compared with the first quartile (multivariate-adjusted hazard ratio=2.84; 95% CI, 1.17 to 6.93). The multivariate-adjusted risks for developing nonembolic infarction (ATIs and LIs) and CHD were significantly elevated in the groups with elevated LDL cholesterol values with and without the metabolic syndrome.

Conclusions—Our findings suggest that an elevated LDL cholesterol level is a significant risk factor for developing ATI as well as CHD, and these associations are independent of the metabolic syndrome. (***Stroke*. 2009;40:382-388.)**

Key Words: epidemiology ■ cholesterol ■ lipoproteins ■ risk factors

Increased blood cholesterol levels are causally related to an increased risk of coronary heart disease (CHD).[1] In contrast, the relation between total cholesterol levels and the risk of stroke remains unclear because of conflicting results reported in the literature.[2,3] The inconsistent results may be due to several reasons. First, because stroke is a heterogeneous syndrome of different etiologic origins, lipid abnormalities may be important for some subtypes of stroke but not for others. An inverse association has been observed between total cholesterol and hemorrhagic stroke,[2,4] and there is a positive association between total cholesterol and ischemic stroke.[2,5] Furthermore, the association may be different for ischemic stroke subtypes.[6] Second, lipoprotein subfractions are considered to exert varying influence on stroke risk.[7] It is possible that the protective effect of HDL cholesterol against stroke weakens the positive association between total cholesterol and stroke in instances where lipoprotein subfractions are counted together. The association between cholesterol and stroke, therefore, needs to be discussed on the basis of stroke subtypes and lipoprotein subfractions.

Together with the results from prospective studies, the positive association between LDL cholesterol level and the risk of CHD has been confirmed by lipid-lowering randomized trials.[8] On the other hand, whereas statins significantly reduced the risk of stroke,[8] the risk reduction for stroke in trials in which subjects were treated with nonstatins was not significant,[9] suggesting that statins involve mechanisms other than cholesterol lowering for the prevention of stroke. Therefore, the true association between LDL cholesterol and the risk of stroke remains unknown. The purpose of this study was to evaluate the association between LDL cholesterol

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level and the development of stroke by its subtypes as well as of CHD in a prospective study of a general Japanese population.

Subjects and Methods

Study Population

Since 1961, we have been conducting a long-term, prospective cohort study of cardiovascular disease (CVD) in the town of Hisayama, a suburb of Fukuoka city in southern Japan. In 1983, a screening survey for the present study was performed in the town. A total of 2548 residents age ≥40 years (80.7% of the total population of this age group) consented to participate in the examination. Of these, 197 subjects were excluded for the following reasons: past history of stroke or myocardial infarction (MI; n=89), blood samples not being collected or collected after a meal (n=86), and excessively high value of triglycerides (≥4.48 mmol/L) for which the Friedewald formula loses its validity[10] (n=22). The remaining 2351 subjects (991 men, 1360 women) were included in this study.

Follow-Up Survey

This population was followed up prospectively for 19 years, from November 1983 through October 2002, by annual health examinations. For subjects who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office for the town, and through the system we gathered information on new events of CVD, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurologic examinations, and ancillary laboratory examinations. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 1 subject was lost to follow-up, 707 subjects died, and 555 subjects (78.5%) underwent autopsy examination.

Definition of Cardiovascular Events

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficits persisting for >24 hours, and the stroke was then classified as either hemorrhagic or ischemic. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke was further divided into 4 clinical categories: atherothrombotic infarction (ATI), lacunar infarction (LI), cardioembolic infarction (CEI), and undetermined subtype of ischemic stroke (UND), based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org10172 in Acute Stroke Treatment (TOAST) Study[12] and the Cerebral Embolism Task Force.[13]

Details of the diagnostic criteria for ischemic stroke subtypes have been described previously.[14] In brief, ATI was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. LI was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[13] The category of UND included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings to be significant and used clinical features as reference information. Cases with cerebrovascular diseases with distinct pathology, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma, or moyamoya disease, were excluded from the evaluation.

During the follow-up period, we identified 271 first-ever stroke events. All of the stroke cases underwent morphologic evaluation that included brain imaging and autopsy; 269 subjects (99.3%) underwent brain imaging studies, and autopsies were performed on 128 subjects of 157 deceased stroke cases (81.5%), including 2 subjects who were not examined by brain imaging. When sufficient clinical and morphologic information was obtained, a diagnosis of cerebral infarction subtype was defined as "definite." When the amount of either type of information was insufficient, the diagnosis level was defined as "probable." On the basis of the aforementioned criteria, stroke cases were divided into 80 hemorrhagic strokes and 191 ischemic strokes (51 ATIs, 93 LIs, 46 CEIs, and 1 UND). Among 191 ischemic strokes, 182 were defined as definite and 9 as probable. In this study, we present the data regarding definite and probable stroke cases together, because these combined data were almost identical to those for definite cases only.

The criteria for the diagnosis of CHD included first-ever acute MI, silent MI, sudden cardiac death within 1 hour after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diagnosis of MI was based on detailed clinical information and at least 2 of the following findings: typical clinical symptoms, ECG evidence of MI, elevated cardiac enzymes, or morphologic findings including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes.[15] During the follow-up period, we identified 144 first-ever events of CHD.

Risk Factors

Blood samples were drawn after an overnight fast of at least 12 hours. All measurements were done within 24 hours after venipuncture in the central study laboratory (Japan Medical Laboratory Inc, Fukuoka, Japan), which participated in the Centers for Disease Control and Prevention Lipid Standardization Program. Total cholesterol and triglyceride levels were measured enzymatically. Measurement of HDL cholesterol was performed after precipitation of VLDL and LDL with dextran sulfate and magnesium. LDL cholesterol concentration was calculated with the Friedewald formula.[10] Plasma glucose levels were determined by the glucose oxidase method. Sitting blood pressure (BP) was measured with a sphygmomanometer 3 times at the right upper arm after at least 5 minutes of rest, and the mean of the 3 measurements was used in the analysis. Hypertension was defined as a BP ≥140/90 mm Hg and/or current treatment with antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3-1), ST-segment depression (Minnesota codes 4-1,2,3), or atrial fibrillation (Minnesota code 8-3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m^2) was calculated. Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a questionnaire. Alcohol consumption and smoking habits were classified as either current use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times per week during their leisure time were designated the regular-exercise group. We defined the presence of the metabolic syndrome according to the National Cholesterol Education Program Expert Panel criteria[16] with a minor modification. The presence of the metabolic syndrome was based on the existence of 3 or more of the following components: (1) BMI ≥25 kg/m^2 as a substitute for waist circumference[17]; (2) fasting triglyceride concentration ≥1.68 mmol/L; (3) HDL cholesterol concentration <1.03 mmol/L in men and <1.29 mmol/L in women; (4) BP ≥130/85 mm Hg or use of antihypertensive drugs; and (5) fasting plasma glucose value ≥6.1 mmol/L or current use of antidiabetic drugs.

Statistical Analysis

To analyze LDL cholesterol level as a categorical variable, we classified the subjects into 4 groups according to quartiles of LDL

Table 1. Age- and Sex-Adjusted Mean Values or Frequencies of Risk Factors for CVD According to LDL Cholesterol Quartiles at Baseline

	Quartile of LDL Cholesterol Levels, mmol/L				
Risk Factor	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Men, %	57.4	44.1	39.2	31.5	<0.001
Age, y	56±11	57±11	57±11	59±11	<0.001
Total cholesterol, mmol/L	4.03±0.57	4.81±0.41	5.40±0.43	6.45±0.68	<0.001
HDL cholesterol, mmol/L	1.36±0.42	1.35±0.36	1.34±0.37	1.31±0.33	<0.001
Triglycerides, mmol/L	1.15±0.75	1.07±0.51	1.12±0.53	1.32±0.58	<0.001
Fasting blood glucose, mmol/L	4.66±0.92	4.75±0.96	4.76±0.93	4.96±1.14	<0.001
Systolic BP, mm Hg	132±22	132±21	135±22	138±21	<0.001
Diastolic BP, mm Hg	81±12	81±12	82±11	83±10	<0.001
Hypertension, %	39.7	41.4	43.8	48.5	0.01
ECG abnormalities,* %	20.6	19.4	21.0	18.4	0.12
BMI, kg/m^2	21.9±3.0	22.2±3.1	23.0±3.1	23.5±3.1	<0.001
Current drinking, %	42.2	33.3	31.8	27.9	<0.001
Current smoking, %	30.7	28.5	28.3	26.5	<0.001
Regular exercise,† %	9.0	7.9	9.5	5.7	0.03

Data are mean±SD or percent. Percentage of men was age adjusted. Mean age was sex adjusted.

*Minnesota codes 3–1; 4–1, –2, –3; or 8–3.

†Engaging in sports or other forms of exertion regularly ≥3 times per week during leisure time.

cholesterol level: ≤2.65, 2.66 to 3.24, 3.25 to 3.88, and ≥3.89 mmol/L. Serum triglyceride levels were logarithmically transformed to improve the skewed distribution. Age- and sex-adjusted mean values of the possible risk factors were calculated by the ANCOVA method, and their trends across LDL cholesterol levels were tested by multiple-regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. The incidences of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method according to 10-year age groups. Differences in age- and sex-adjusted incidences between LDL cholesterol quartiles were tested by Cox proportional-hazards regression analysis. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% CIs were also calculated by the Cox proportional-hazards model. All statistical analyses were performed with the SAS program package. $P<0.05$ was considered statistically significant in all analyses.

Results

The age- and sex-adjusted mean values or frequencies of risk factors for CVD are listed by quartiles of LDL cholesterol levels at baseline in Table 1. The frequencies of male sex, current drinking, current smoking, and regular exercise and the mean values of HDL cholesterol declined with increasing LDL cholesterol level, whereas mean values of age, total cholesterol, triglycerides, fasting blood glucose, systolic and diastolic BPs, BMI, and frequency of hypertension significantly increased with rising LDL cholesterol level. The frequency of ECG abnormalities was not different among serum LDL cholesterol levels.

Table 2 shows the age- and sex-adjusted incidences of CVD according to quartiles of LDL cholesterol levels. No significant associations were observed between LDL cholesterol levels and the incidences of stroke, whether ischemic or hemorrhagic. In regard to subtypes of ischemic stroke, the incidences of ATI and LI significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATI and=0.02 for LI), and there were significant differences between the first and fourth quartiles of LDL cholesterol for both subtypes (age- and sex-adjusted HR=2.31; 95% CI, 1.03 to 5.16; $P=0.04$ for ATI; age- and sex-adjusted HR=2.00; 95% CI, 1.05 to 3.80; $P=0.03$ for LI; Table 3). No such association was observed for CEI. The incidence of CHD also significantly increased with increasing LDL cholesterol level (P for trend <0.001), and compared with the first quartile, the incidence was significantly higher in the third (age- and sex-adjusted HR=1.77; 95% CI, 1.07 to 2.91; $P=0.03$; Table 3) and fourth (age- and sex-adjusted HR=2.00; 95% CI, 1.22 to 3.28; $P=0.006$) quartiles.

As shown in Table 3, the positive associations between LDL cholesterol level and risk of ATI and CHD remained significant even after adjustment for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise (P for trend=0.02 for ATI and=0.03 for CHD). Compared with the first quartile, the risk of ATI was significantly high in the fourth quartile after adjustment for the aforementioned confounding factors (multivariate-adjusted HR=2.84; 95% CI, 1.17 to 6.93; $P=0.02$). On the other hand, the negative association between LDL cholesterol and the risk of CEI appeared to be significant after multivariate adjustment (P for trend=0.03), and the risk of CEI was significantly lower in the fourth quartile than in the first quartile (multivariate-adjusted HR=0.34; 95% CI, 0.12 to 0.96; $P=0.04$). A similar association was observed when LDL cholesterol was examined on a continuous scale.

Because not only LDL cholesterol but also other metabolic factors may be strong risk factors for CVD, we examined the combined as well as the separate effects of elevated LDL cholesterol level and the metabolic syndrome on the development of selected CVDs. As shown in the Figure, we

Table 2. Age- and Sex-Adjusted Incidences (per 1000 Person-Years) of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L				
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Stroke					
No. of events	56	62	74	79	
Age- and sex-adjusted incidence	7.4	8.1	10.1	10.2	0.13
Ischemic stroke					
No. of events	37	47	47	60	
Age- and sex-adjusted incidence	4.9	6.3	6.8	7.9	0.07
Atherothrombotic					
No. of events	9	12	9	21	
Age- and sex-adjusted incidence	1.2	1.6	1.2	3.3*	0.03
Lacunar					
No. of events	14	21	25	33	
Age- and sex-adjusted incidence	2.0	2.6	2.9	3.8*	0.02
Cardioembolic					
No. of events	14	14	12	6	
Age- and sex-adjusted incidence	1.7	2.1	2.4	0.8	0.07
Hemorrhagic stroke					
No. of events	19	15	27	19	
Age- and sex-adjusted incidence	2.6	1.8	3.3	2.3	0.95
CHD					
No. of events	25	28	43	48	
Age- and sex-adjusted incidence	3.4	3.4	5.5*	6.6†	<0.001

*$P<0.05$, †$P<0.01$ vs lowest quartile.

estimated the HRs for the occurrence of nonembolic infarction, including ATI and LI, as well as of CHD, by dividing the subjects into 4 groups according to the presence or absence of high LDL cholesterol levels (the fourth quartile, ≥3.89 mmol/L for nonembolic infarction; the third and fourth quartiles, ≥3.25 mmol/L for CHD) and the metabolic syndrome after adjustments for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Compared with a reference group with neither high LDL cholesterol levels nor the metabolic syndrome, the risk of developing nonembolic infarction was significantly high in the group with high LDL cholesterol levels alone and in the group with both high LDL cholesterol levels and the metabolic syndrome, whereas it was marginally significant for the group with the metabolic syndrome alone. Similarly, the risk for the development of CHD was elevated in both the group with high LDL cholesterol without the metabolic syndrome and the group with high LDL cholesterol and the metabolic syndrome. The risk of CHD was also significant for the group with the metabolic syndrome alone.

Discussion

In a long-term, prospective study of a general Japanese population, we demonstrated positive and significant associations between serum LDL cholesterol level and risk for the development of ATI and CHD. These associations remained unchanged even after adjustment for other lipid fractions as well as other confounding factors, namely, age, sex, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. In addition, the impact of high LDL cholesterol on CVD appeared to be similar to that of the metabolic syndrome. On the other hand, the association between LDL cholesterol level and the risk of CEI was negative and significant after adjusting for the aforementioned risk factors. To our knowledge, this is the first prospective cohort study to investigate the association between LDL cholesterol and the development of subtypes of ischemic stroke.

Several prospective studies have investigated the association between LDL cholesterol and ischemic stroke, but the results were not unanimous. The Cardiovascular Health Study[18] reported a positive association between LDL cholesterol and the risk of ischemic stroke, whereas the Atherosclerosis Risk in Communities Study[19] and the Framingham Study[20] found no clear associations. In the present analysis, LDL cholesterol level was not clearly associated with the risks of stroke and ischemic stroke, but these associations were heterogeneous across ischemic stroke subtypes. Because LI and CEI seem to have a less potent relation with elevated LDL cholesterol,[21,22] inclusion of those subtypes may mask the positive association between LDL cholesterol and ATI. This heterogeneity in the associations of LDL cholesterol level and ischemic stroke subtypes may be a reason for the controversial results obtained from previous studies that investigated the outcome of "total" ischemic stroke.

Table 3. Age-, Sex-, and Multivariate-Adjusted HRs and 95% CIs for the Development of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L					
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend	Continuous Scale
Stroke						
No. of events	56	62	74	79		
Age- and sex-adjusted HR (95% CI)	1.0	0.96 (0.66–1.37)	1.12 (0.84–1.69)	1.23 (0.86–1.75)	0.13	1.08 (0.95–1.23)
Multivariate-adjusted HR (95% CI)	1.0	0.94 (0.64–1.38)	1.15 (0.79–1.67)	1.23 (0.84–1.81)	0.16	1.07 (0.93–1.24)
Ischemic stroke						
No. of events	37	47	47	60		
Age- and sex-adjusted HR (95% CI)	1.0	1.08 (0.70–1.67)	1.17 (0.75–1.80)	1.45 (0.95–2.21)	0.07	1.15 (0.99–1.35)
Multivariate-adjusted HR (95% CI)	1.0	1.05 (0.66–1.66)	1.05 (0.66–1.68)	1.35 (0.85–2.14)	1.19	1.11 (0.94–1.31)
Atherothrombotic						
No. of events	9	12	9	21		
Age- and sex-adjusted HR (95% CI)	1.0	1.14 (0.48–2.71)	0.98 (0.39–2.50)	2.31 (1.03–5.16)*	0.03	1.51 (1.14–1.99)§
Multivariate-adjusted HR (95% CI)	1.0	1.35 (0.54–3.35)	1.19 (0.45–3.17)	2.84 (1.17–6.93)*	0.02	1.60 (1.19–2.16)§
Lacunar						
No. of events	14	21	25	33		
Age- and sex-adjusted HR (95% CI)	1.0	1.29 (0.65–2.54)	1.58 (0.81–3.05)	2.00 (1.05–3.80)*	0.02	1.23 (1.00–1.53)
Multivariate-adjusted HR (95% CI)	1.0	1.19 (0.57–2.50)	1.41 (0.69–2.89)	1.69 (0.83–3.43)	0.11	1.13 (0.90–1.43)
Cardioembolic						
No. of events	14	14	12	6		
Age- and sex-adjusted HR (95% CI)	1.0	0.83 (0.39–1.75)	0.80 (0.37–1.75)	0.39 (0.15–1.04)	0.07	0.71 (0.51–1.00)
Multivariate-adjusted HR (95% CI)	1.0	0.75 (0.34–1.63)	0.59 (0.25–1.38)	0.44 (0.12–0.96)*	0.03	0.64 (0.44–0.94)‡
Hemorrhagic stroke						
No. of events	19	15	27	19		
Age- and sex-adjusted HR (95% CI)	1.0	0.69 (0.35–1.36)	1.24 (0.68–2.24)	0.83 (0.43–1.59)	0.95	0.94 (0.74–1.20)
Multivariate-adjusted HR (95% CI)	1.0	0.71 (0.35–1.47)	1.41 (0.75–2.65)	1.01 (0.50–2.05)	0.53	1.02 (0.79–1.33)
CHD						
No. of events	25	28	43	48		
Age- and sex-adjusted HR (95% CI)	1.0	1.02 (0.60–1.76)	1.77 (1.07–2.91)*	2.00 (1.22–3.28)†	<0.001	1.29 (1.08–1.53)§
Multivariate-adjusted HR (95% CI)	1.0	1.01 (0.56–1.80)	1.68 (0.99–2.84)	1.57 (0.91–2.73)	0.03	1.15 (0.95–1.39)

Multivariate adjustment was made for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. For the continuous scale, HR is given for each 1-mmol/L increase in LDL cholesterol.

*$P<0.05$, †$P<0.01$ vs lowest quartile; ‡$P<0.05$, §$P<0.01$.

The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.[23,24] Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.

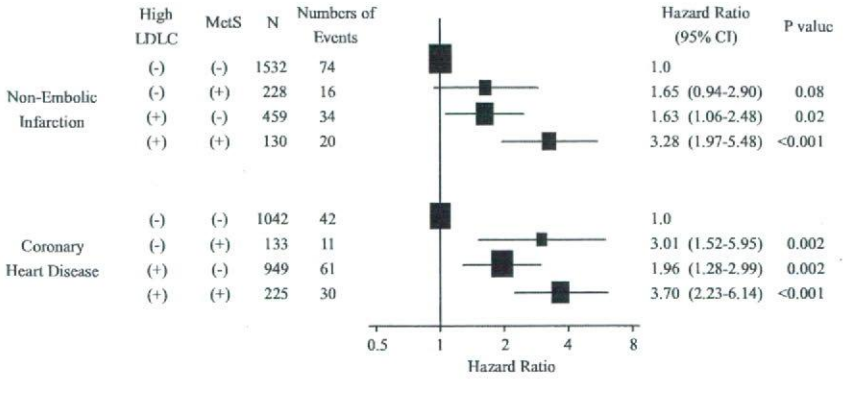

Figure. Multivariate-adjusted HRs for the development of nonembolic infarction and CHD according to the presence or absence of high LDL cholesterol and the metabolic syndrome. Multivariate adjustment was made for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Centers of the boxes are placed at the estimates of HRs. Horizontal lines indicate 95% CIs, and sizes of boxes are proportional to the numbers of events. LDLC indicates LDL cholesterol; MetS, metabolic syndrome.

In our cohort, the association between LDL cholesterol and the risk of LI was no longer significant after multivariate adjustment, suggesting that elevated LDL cholesterol was not an independent risk factor for the development of LI. Our previous report showed that multiple risk factors were related to the occurrence of LI,[14] and case-control studies on the relation between LDL cholesterol level and LI have reported varied associations.[21,22,25] One study reported a significant association between elevated LDL cholesterol and the risk of LI,[25] another study observed lower LDL cholesterol levels in LI cases,[22] and another study found no significant association.[21] Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion.[26] Lipohyalinosis is a vasculopathy caused by hypertension,[26] whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol,[23,24] but cardioembolism seems less related to elevated LDL cholesterol.[22,25] These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

An inverse relation between LDL cholesterol level and the risk of CEI was observed in our earlier population in the 1960s,[14] and the same association was found in the present investigation after adjustment for confounding factors. Although the reason for this association is unknown, a plausible explanation is that a lowered cholesterol level might increase the risk of CEI through the increased occurrence of atrial fibrillation,[27] a predominant risk factor for CEI. Additional clinical and experimental evidence is needed to elucidate the mechanism underlying this association.

The results of previous prospective studies of the association between LDL cholesterol and hemorrhagic stroke have been inconsistent; a significant inverse association was reported in women in the Framingham Study,[20] whereas a nonsignificant association was observed in the Cardiovascular Health Study.[18] Lipid-lowering trials recently conducted in Japan[28,29] and a meta-analysis of >90 000 subjects enrolled in statin trials[8] found no apparent increase in the risk of hemorrhagic stroke. A nonsignificant association between LDL cholesterol and the risk of hemorrhagic stroke observed in our data was in accord with the findings of a previous prospective study[18] and intervention trials.[8,28,29]

Several prospective studies conducted in Western countries have reported positive associations between LDL cholesterol and the risk of CHD.[30] Among Japanese, no study has investigated the association between LDL cholesterol level and the risk of CHD, but several prospective studies have shown that total cholesterol is a strong risk factor for CHD.[31,32] The findings obtained from the present analysis support the results from those prospective studies and, for the first time, have demonstrated a positive association between calculated LDL cholesterol and the risk of CHD in a general Japanese population.

The metabolic syndrome has been shown to be a clear risk factor for CVD,[33] but LDL cholesterol level is not involved in the definition of the metabolic syndrome. In the present analysis, comparable and independent effects were observed for elevated LDL cholesterol and the metabolic syndrome on the risks of nonembolic infarction and CHD. The highest risk was observed for the subgroup with both an elevated LDL cholesterol value and the metabolic syndrome. Similar results were found in a prospective study of a Danish cohort.[34] All of these results imply that management of LDL cholesterol as well as the metabolic syndrome is important for the prevention of ischemic stroke and CHD.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, almost perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD, including ischemic stroke subtypes. One limitation of our study is that our findings are based on a 1-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the relation observed in the present study, because a random misclassification of such nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Another limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation. This equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and CVD. It is unlikely that the bias of LDL cholesterol values that occurred through calculation, if any, would have strengthened the association between LDL cholesterol and ATI or CHD observed in the present analysis.

In conclusion, we have shown that elevated LDL cholesterol is a significant risk factor for developing ATI as well as CHD in a general Japanese population. Because LDL cholesterol level is independent of the metabolic syndrome for the development of CVD, lowering a patient's LDL cholesterol level should be considered together with treatment of other metabolic disorders for the prevention of CVD.

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Disclosures

None.

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Original Article

Differences in Insulin Action and Secretion, Plasma Lipids and Blood Pressure Levels between Impaired Fasting Glucose and Impaired Glucose Tolerance in Japanese Subjects

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We examined insulin action/secretion and cardiovascular disease risk factors in Japanese subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) who were not taking any medications known to affect glucose tolerance, blood pressure (BP) or plasma lipids (PLs). A total of 1,399 subjects received measurements of anthropometry, BP, PLs, and plasma glucose/insulin concentrations during 75 g-oral glucose tolerance test (OGTT). According to 2003 American Diabetes Association criteria, subjects were classified as having normal fasting glucose (NFG)/normal glucose tolerance (NGT) (n=1,173), IFG (n=128), IGT (n=55), and IFG/IGT (n=43). Insulin action was calculated using the HOMA-R (index of hepatic insulin resistance) and Matsuda index (reflects whole body insulin sensitivity). The ratio of the incremental area under the curve of insulin to that of glucose during OGTT ($\Delta AUC_{PI}/\Delta AUC_{PG}$) was used as an index of β-cell function. HOMA-R was higher in IFG (2.3±0.1) and IFG/IGT (2.5±0.2) than in NFG/NGT (1.8±0.03). The Matsuda index was lower in IFG (6.5±0.3), IGT (5.4±0.4) and IFG/IGT (5.1±0.5) than in NFG/NGT (9.6±0.2). $\Delta AUC_{PI}/\Delta AUC_{PG}$ was lower in IGT (0.6±0.05) and IFG/IGT (0.5±0.05) than in IFG (1.4±0.12) or NFG/NGT (1.2±0.03). Mean BP was higher in IGT (100±1.7 mmHg) than in NFG/NGT (91±0.3) or IFG (95±1.1). The plasma triglyceride level was higher in IGT (155±14 mg/dL) and IGT/IFG (173±12) than in IFG (132±7) or NFG/NGT (122±2). In conclusion, 1) whole body insulin sensitivity is decreased in IFG and IGT, with a greater reduction in IGT, 2) hepatic insulin resistance and preserved β-cell function are characteristics of IFG, and 3) higher BP and triglyceride levels are observed in IGT. IGT is more closely associated with risk factors for cardiovascular disease than is IFG. (*Hypertens Res* 2008; 31: 1357–1363)

Key Words: **impaired fasting glucose, impaired glucose tolerance, cardiovascular disease risk factors**

Introduction

Impaired glucose tolerance (IGT) is an intermediate state in the transition from normal glucose tolerance (NGT) to type 2 diabetes. IGT subjects are at high risk for progression to type 2 diabetes, with an annual conversion rate of 5–10%, depending upon the ethnic group (*1–5*). In 1997, the American Diabetes Association (ADA) introduced another intermediate state, impaired fasting glucose (IFG) (*6*), in the transition from NGT to type 2 diabetes. IFG was meant to be analogous to IGT, since subjects with isolated IFG and isolated IGT had similar risk for progression to type 2 diabetes (*1–5*). However, only 45% of subjects with IFG had IGT; conversely,

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Table 1. Clinical Characteristics and Metabolic Measurements

	NFG/NGT	IFG	IGT	IFG/IGT	NFG/NGT *vs.* IFG	NFG/NGT *vs.* IGT	NFG/NGT *vs.* IFG/IGT	IFG *vs.* IGT	IFG *vs.* IFG/IGT	IGT *vs.* IFG/IGT
n	1,173	128	55	43						
Age (years old)	58±0.3	60±0.9	60±1.3	62±1.6						
Gender (male/female)	514/659	64/64	30/25	29/14			<0.01		<0.05	
BMI (kg/m^2)	23.1±0.1	23.8±0.3	23.9±0.4	24.3±0.5						
FPG (mg/dL)	85±0.2	105±0.5	92±0.7	108±1.2	<0.01	<0.01	<0.01	<0.01		<0.01
PG_{60} (mg/dL)	122±0.8	156±2.7	190±4.3	218±4.9	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
PG_{120} (mg/dL)	99±0.4	120±0.8	154±2.1	156±2.0	<0.01	<0.01	<0.01	<0.01	<0.01	
Mean PG (mg/dL)	107±0.5	134±1.5	157±2.4	175±2.7	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
FPI (μU/mL)	8.7±0.2	8.9±0.5	9.9±0.8	9.3±0.9						
PI_{60} (μU/mL)	41±0.9	58±3.6	60±5.0	55±4.4	<0.01	<0.01				
PI_{120} (μU/mL)	27±0.5	32±2.8	57±4.6	38±3.7	<0.05	<0.01	<0.01	<0.01		<0.01
Mean PI (μU/mL)	29±0.6	39±2.3	46±3.4	39±2.9	<0.01	<0.01	<0.05			
Systolic BP (mmHg)	125±0.5	131±1.7	140±2.9	131±3.2	<0.01	<0.01		<0.01		
Diastolic BP (mmHg)	74±0.3	75±0.9	79±1.3	77±1.7		<0.01				
Mean BP (mmHg)	91±0.3	94±1.0	100±1.7	95±2.0		<0.01		<0.05		
Total cholesterol (mg/dL)	188±0.9	194±2.8	196±3.8	190±4.4						
HDL cholesterol (mg/dL)	56±0.4	54±1.1	53±2.1	51±2.2						
LDL cholesterol (mg/dL)	108±0.9	113±2.7	112±4.0	104±4.0						
TG (mg/dL)	122±2.5	132±7.2	155±13.6	173±12.3		<0.01	<0.01			
TG/HDL cholesterol ratio	2.5±0.1	2.7±0.2	3.4±0.4	3.9±0.4		<0.01	<0.01		<0.01	

Data are means±SEM. *p* values indicate significance of differences among pairs of the groups analyzed by ANOVA. BMI, body mass index; FPG, fasting plasma glucose; PG, plasma glucose; $PG_{60\,(120)}$, PG at 60 (120) min; FPI, fasting plasma insulin; PI, plasma insulin; $PI_{60\,(120)}$, PI at 60 (120) min; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; NFG, normal fasting glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose.

<25% of subjects with IGT had IFG (*2*, *3*, *7–11*). The partial overlap between IFG and IGT suggests that different pathophysiological mechanisms contribute to the disturbances in glucose homeostasis. However, the differences in pathophysiological mechanisms between IGT and IFG had not been fully defined. Some studies reported that the primary abnormality in IFG was insulin resistance, while IGT was more associated with impaired β-cell function (*12–19*). Other studies have reported opposite results (*20–24*). In 2003, the ADA introduced new diagnostic criteria for IFG based on the receiver operator curve analysis of several prospective epidemiological studies (*25*). As a result of this analysis, the criteria of the fasting plasma glucose (FPG) concentration for IFG was reduced from 110 to 100 mg/dL, and isolated IFG was defined as an FPG of 100–125 mg/dL with 2-h plasma glucose (PG) < 140 mg/dL during the 75 g-oral glucose tolerance test (OGTT) (*25*). Using these new criteria, Abdul-Ghani *et al.* demonstrated that Mexican American and Caucasian subjects with IGT and IGT/IFG had significantly greater reductions in peripheral (muscle) insulin sensitivity and insulin secretion compared to subjects with IFG (*26*). However, the subject population was obese (body mass index [BMI] >30 kg/m^2) and 3/4 of the subjects were of Hispanic descent (*26*). Little information is available about differences in insulin action and insulin secretion in other ethnic groups with IFG, IGT, and IFG/IGT and in subjects whose BMI is in the normal weight range. Therefore, one aim of the present study was to examine insulin sensitivity and secretion in healthy, normal-weight Japanese subjects who were not taking any medications known to affect glucose tolerance, blood pressure, or lipids levels.

It has also been reported that IGT is associated with an increased prevalence of cardiovascular risk factors (*27–30*) and cardiovascular events (*30*, *31*), whereas IFG is less strongly associated with cardiovascular events and mortality (*30*, *31*). Therefore, a second aim of this study was to examine the association between cardiovascular risk factors (blood pressure and plasma lipids) and IFG, IGT, and IFG/IGT using the 2003 revised ADA criteria in Japanese subjects.

Methods

We have been carrying out a medical examination and epidemiological investigation of cardiovascular disease in the towns of Tanno and Sobetsu, Hokkaido, Japan since 1976 (*32*). From 2,027 citizens who had undergone medical examination and received measurements of anthropometry, blood pressure, plasma lipids, and PG/plasma insulin (PI) concen-

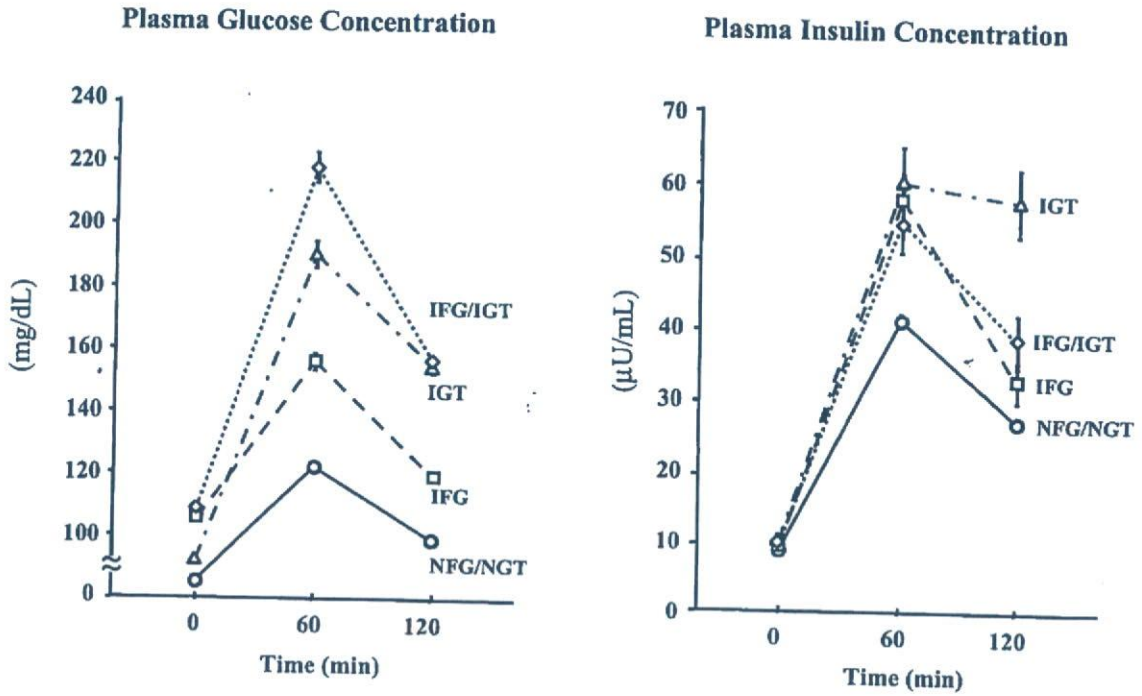

Fig. 1. *Plasma glucose (PG) and insulin (PI) concentrations during the 75 g-OGTT in subjects with normal fasting glucose and glucose tolerance (NFG/NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and IFG plus IGT (IFG/IGT).*

trations during 75 g-OGTT in the town of Tanno and Sobetsu, we selected every healthy subject ($n=1,399$) who was not taking any medications known to affect glucose tolerance, blood pressure, and plasma lipids levels, and who did not have a history of diabetes. All study subjects were in good general health without evidence of cardiac, hepatic, renal or other chronic diseases as determined by medical history, complete blood cell count (CBC), routine chemistries and ECG. At 8 AM, after a 10-h overnight fast, height and weight were measured and BMI was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 min in the reclining position with an automated blood pressure recorder (OMRON HEM 907; OMRON HEALTHCARE, Kyoto, Japan). Blood samples for measurement of fasting plasma lipids (total cholesterol, triglyceride [TG], high-density lipoprotein [HDL] cholesterol) were obtained through an indwelling catheter. Subjects then ingested 75 g of glucose and blood for measurement of PG and PI concentrations were obtained at 0, 60, and 120 min. Plasma total cholesterol, TG, and HDL cholesterol concentrations were measured enzymatically on an AU5200 autoanalyzer (OLYMPUS, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald equation. PG was measured using the glucose oxidase method, and PI was measured using RIA beads (Dinabot, Tokyo, Japan).

Insulin sensitivity indices were calculated from OGTT using the HOMA-R (*26, 33*) and Matsuda index [10,000/{(FPG × FPI) × (mean PG × mean PI)}$^{1/2}$] (*26, 34*). To evaluate β-cell function, the insulinogenic index was calculated as the incremental area under the curve (AUC) of PI (ΔAUC_{PI}) divided by the incremental AUC of PG (ΔAUC_{PG}) during a 0–120 min (total) time period of the OGTT (*26, 35*). The insulin secretion/insulin resistance (disposition) index ($\Delta AUC_{PI}/\Delta AUC_{PG} \times$ Matsuda index) also was determined to provide a measure of β-cell function (*19, 26*). Incremental AUCs of plasma insulin and glucose were calculated according to the trapezoid rule.

Statistical analysis was performed with StatView for Windows, v 5.0 (SAS Institute Inc., Cary, USA). Comparisons between groups were performed using analysis of variance with Scheffe post-hoc testing when appropriate. The χ^2 test was used for comparing proportions between groups. Stepwise multiple regression analysis was performed to examine the multiple correlations among variables. All data are presented as the mean value±SEM. Values of $p<0.05$ were considered statistically significant.

Results

The clinical characteristics and metabolic parameters of each group are summarized in Table 1. The IFG/IGT group had a higher percentage of males compared with the other three

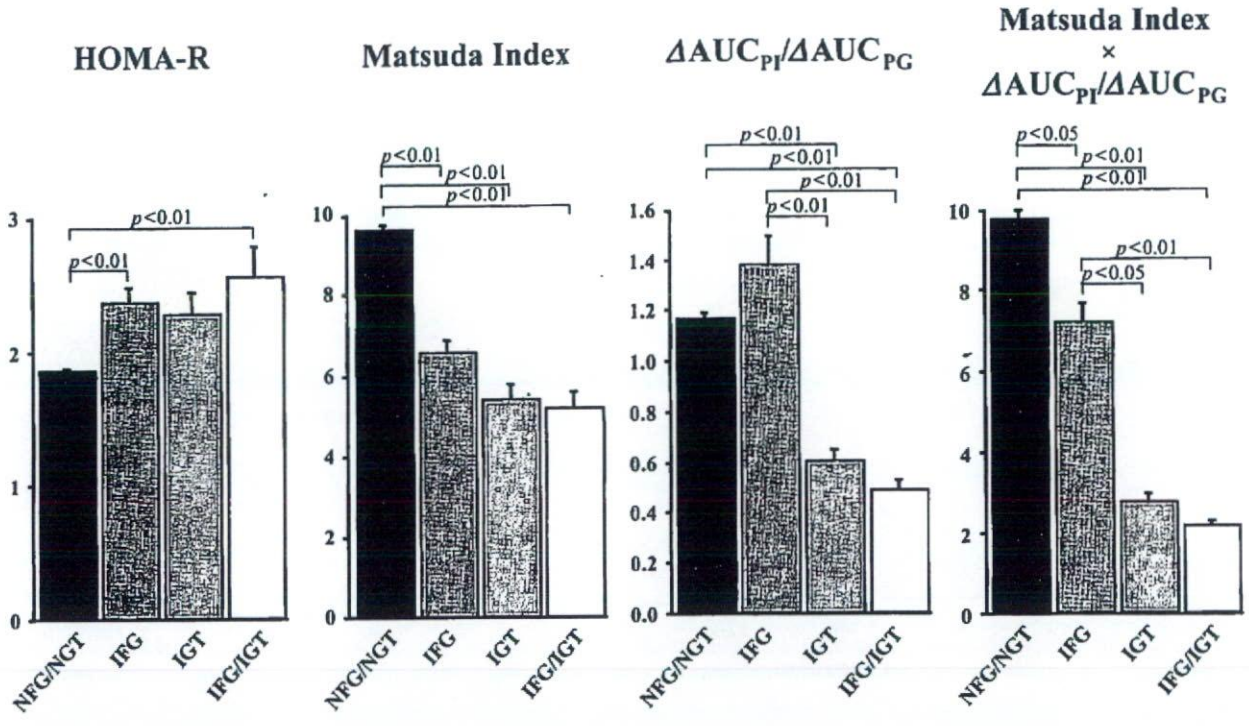

Fig. 2. *HOMA-R, Matsuda index [10,000/{(FPG × FPI) × (mean PG × mean PI)}$^{1/2}$], ratio of incremental area under the curve (AUC) of PI to incremental AUC of PG [$\Delta AUC_{PI}/\Delta AUC_{PG}$], and Matsuda index × $\Delta AUC_{PI}/\Delta AUC_{PG}$ during OGTT in subjects with normal fasting glucose and glucose tolerance (NFG/NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), and IFG plus IGT (IFG/IGT). p values indicate significant differences among the groups.*

groups. The four groups were similar in age, BMI, and fasting plasma levels of total-, HDL- and LDL-cholesterol. By definition subjects with isolated IFG and combined IFG/IGT had a significantly increased FPG compared to the normal fasting glucose (NFG)/NGT and isolated IGT groups. PG excursions during the OGTT rose progressively from NFG/NGT to IFG to IGT to IFG/IGT, and PG in each group was significantly higher than in the preceding group (Fig. 1 and Table 1). PI excursions during the OGTT were similar in IFG/IGT and IFG and both were significantly greater than in NFG/NGT. PI at 60 min (PI_{60}) during the OGTT was significantly higher in IFG and IGT than in NFG/NGT, while PI at 120 min (PI_{120}) and mean PI during the OGTT were significantly higher in IFG, IGT, and IFG/IGT than in NFG/NGT. The PI_{120} was significantly higher in IGT than in IFG and IFG/IGT. Blood pressure was significantly higher in IGT compared with NFG/NGT or IFG. Also, only SBP was significantly higher in IFG than in NFG/NGT. The prevalence of hypertension (SBP≥140 mmHg or DBP≥90 mmHg) in each group was 20% (235/1,173) in NFG/NGT, 29% (37/128) in IFG, 47% (26/55) in IGT, and 37% (16/43) in IFG/IGT, respectively. The TG concentration and TG/HDL cholesterol ratio were significantly higher in the IGT or IGT/IFG group than in the NFG/NGT group. Furthermore, the IGT/IFG group had a higher TG/HDL cholesterol ratio compared with the IFG group. The differences in metabolic parameters and blood pressure remained even after significant adjustment for gender, age, and BMI.

HOMA-R, an index of hepatic insulin resistance, was significantly higher in IFG (2.3±0.1) and IFG/IGT (2.5±0.2) than in NFG/NGT (1.8±0.04) (Fig. 2). The Matsuda index, a measure of whole body (especially muscle) insulin sensitivity, was significantly reduced in the IFG (6.5±0.3), IGT (5.4±0.4) and IFG/IGT (5.1±0.5) groups compared with the NFG/NGT group (9.5±0.2). $\Delta AUC_{PI}/\Delta AUC_{PG}$, an index of β-cell function, was significantly lower in IGT (0.6±0.05) and IFG/IGT (0.5±0.04) compared with IFG (1.4±0.1) or NFG/NGT (1.2±0.03). The insulin secretion/insulin resistance index of β-cell function ($\Delta AUC_{PI}/\Delta AUC_{PG}$ × Matsuda index) was significantly lower in the IFG (7.1±0.5) compared to the NGT group and was further and significantly reduced in the IGT (2.7±0.2) and IFG/IGT (2.1±0.2) groups compared with both the NFG/NGT (9.7±0.2) and IFG (7.1±0.5) groups.

The predictors of mean blood pressure, TG, and TG/HDL cholesterol ratio were examined in backward stepwise regression analysis using age, gender (male), BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PI_{120} during the OGTT as independent variables (Table 2). Increased age, BMI, PG_{120} and PI_{120}, and

Table 2. Multiple Regression Analyses for Blood Pressure, Triglyceride Level, and TG/HDL Cholesterol Ratio

Variables	Standard coefficient	SEM	*p* value
Positive predictors of mean blood pressure			
Age	0.129	0.026	<0.0001
Gender (male)	0.082	0.586	0.0014
BMI	0.170	0.105	<0.0001
PG_{120}	0.161	0.016	<0.0001
PI_{120}	0.082	0.015	0.0046
Positive predictors of triglyceride (TG) level			
Gender (male)	0.181	4.395	<0.0001
BMI	0.169	0.793	<0.0001
PG_{120}	0.064	0.114	0.0156
PI_{120}	0.147	0.071	<0.0001
Predictors of TG/HDL cholesterol ratio			
Gender (male)	0.201	0.110	<0.0001
BMI	0.200	0.020	<0.0001
FPI	−0.063	0.011	0.0199
PI_{60}	0.182	0.002	<0.0001
PI_{120}	0.074	0.003	0.0171

Evaluated parameters: age, gender, BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PI_{120} during 75 g-OGTT. TG, triglyceride; HDL, high-density lipoprotein; BMI, body mass index; PG_{120}, plasma glucose at 120 min; $PI_{60\,(120)}$, plasma insulin at 60 (120) min; OGTT, oral glucose tolerance test.

male gender were positive predictors of the increase in mean blood pressure (adjusted $r^2=0.12$, $p<0.0001$). When performing the same analysis for SBP or DBP, increased age, BMI, PG_{120} and PI_{120} were positive predictors of the increase in SBP (adjusted $r^2=0.12$, $p<0.0001$), and increased BMI, PG_{120} and PI_{60}, PI_{120} and male gender were positive predictors of the increase in DBP (adjusted $r^2=0.10$, $p<0.0001$). Increased BMI, PG_{120}, PI_{60}, and male gender were independent positive predictors of the increase in plasma TG (adjusted $r^2=0.11$, $p<0.0001$). BMI, PI_{60} and PI_{120}, decreased FPI, and male gender were independent positive predictors of the increase in TG/HDL cholesterol ratio (adjusted $r^2=0.15$, $p<0.0001$) (Table 2). Inversely, BMI, PI_{60} and PI_{120}, decreased FPI, and male gender were independent positive predictors of the decrease in HDL cholesterol (adjusted $r^2=0.13$, $p<0.0001$).

Discussion

In the present study, we investigated the pathophysiological disturbances in Japanese subjects with IFG, IGT, and IFG/IGT. HOMA-R was significantly higher in subjects with IFG with or without accompanying IGT compared to those with NFG/NGT. The HOMA-R index represents the product of the FPG and FPI concentrations (*33*). Since hepatic glucose production (HGP) is the primary determinant of the FPG concentration (*36*), and the fasting plasma insulin concentration is the primary regulator of HGP (*37*), HOMA-R primarily reflects hepatic insulin resistance. Thus, our results indicate that Japanese individuals with IFG are characterized by hepatic insulin resistance. The Matsuda index [10,000/{(FPG × FPI) × (mean PG × mean PI)}$^{1/2}$] was decreased in the IFG, IGT, and IFG/IGT groups compared to the NFG/NGT group, with a greater reduction in IGT ($p=0.03$) with or without IFG ($p=0.05$). The Matsuda index is strongly correlated with insulin-stimulated total body glucose disposal, which primarily reflects muscle insulin sensitivity, during the euglycemic insulin clamp (*26*, *34*). Thus, IGT can be characterized as a state of muscle insulin resistance. β-Cell function, expressed as $\Delta AUC_{PI}/\Delta AUC_{PG}$ and $\Delta AUC_{PI}/\Delta AUC_{PG}$ × Matsuda index was more severely reduced in IGT with or without IFG compared with both NFG/NGT and IFG. Thus, Japanese subjects with IGT are characterized by both muscle insulin resistance and impaired insulin secretion. In contrast, IFG represents a state of hepatic insulin resistance with impaired early (0–60 min) but normal to slightly increased late phase (60–120 min) insulin secretion. These distinct metabolic disturbances in hepatic/muscle insulin sensitivity and β-cell function in nondiabetic healthy Japanese subjects with IFG, IGT, and IFG/IGT are similar to those reported in Mexican-American subjects (*26*). However, the severity of hepatic and muscle insulin resistance and the compensatory plasma insulin response following glucose ingestion is much higher in Mexican-Americans (see figure 1 and table 1 in Abdul-Ghani *et al.* (*26*)). The difference in severity in the insulin resistance and hyperinsulinemia most likely reflects the greater obesity and/or differences in genetic background in the Mexican-American *vs*. Japanese individuals.

We also compared the prevalence of cardiovascular risk factors in healthy Japanese subjects with IFG, IGT, and IFG/IGT. Of note, no subject was taking any medications known to affect glucose metabolism, blood pressure, or plasma lipid levels. Blood pressure was significantly higher in IGT than in either NFG/NGT or IFG. TG and the TG/HDL cholesterol ratio were significantly higher in IGT and IFG/IGT than in either NFG/NGT or isolated IFG. These findings in Japanese subjects are consistent with previous publications demonstrating an increased prevalence of cardiovascular risk factors and cardiovascular events in subjects with IGT, whereas IFG (defined by the 1997 ADA criteria) appears to be much less strongly associated with cardiovascular disease (*27–31*). The results in the present study, in which IFG and IGT were employed in healthy Japanese subjects, are consistent with the results of these previous reports. However, several studies have reported (using the 1997 ADA criteria) that both IFG and IGT were associated with an increased prevalence of cardiovascular risk factors (*38–40*). Using the 2003 ADA criteria for IFG, Kim *et al.* (*41*) did not observe an increased prevalence of cardiovascular risk factors. Because of these conflicting results, we performed multiple regression analysis to define which variables best predicted the presence of cardiovascular risk factors in our population of healthy Japanese subjects. Among the independent variables (age, gender, BMI, FPG, PG_{60}, PG_{120}, FPI, PI_{60}, and PGI_{120}), multiple stepwise regression analysis revealed that male gender, increased age, higher BMI, and elevated PG_{120} and PI_{120} were independently and positively associated with increased blood pressure. Many of the same variables (male gender, BMI, higher level of PG_{60} and PI_{120}) were independently and positively associated with elevated plasma TG levels and an increased TG/HDL cholesterol ratio. In summary, male gender, obesity, elevated postprandial but not fasting levels of PG and insulin concentrations are associated with cardiovascular risk factors (higher blood pressure and TG, increased TG/HDL cholesterol ratio) in pre-diabetic individuals.

In conclusion, subjects with IFG predominantly manifest hepatic insulin resistance leading to higher FPG and normal/near-normal indices of β-cell function, while subjects with IGT predominantly manifest peripheral (muscle) insulin resistance combined with impaired β-cell function leading to higher elevations in PG concentration during the postprandial state. Elevated blood pressure, plasma TG, and TG/HDL cholesterol ratio, components of the metabolic or insulin syndrome, are more commonly observed in Japanese subjects with IGT than in those with IFG.

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Original Article

Incidence of Hypertension in Individuals with Abdominal Obesity in a Rural Japanese Population: The Tanno and Sobetsu Study

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Although abdominal obesity (AO) assessed by waist circumference (WC) is an important component of the metabolic syndrome (MetS), the usefulness of AO as a predictor of hypertension (HT) is not known. In this study, we investigated the incidence of HT in residents of two rural communities in Japan. The subjects were 187 men and 209 women selected from 712 residents who had undergone medical examinations in the towns of Tanno and Sobetsu, Hokkaido, in 1994 and 2002. Participants with HT in 1994 were excluded. Participants with AO were determined according to the WC criteria in the Japanese definition of MetS (≥85 cm for men, ≥90 cm for women). The participants were divided into two groups: a non-AO group and an AO group. We compared the incidence of HT between the two groups and found a significantly higher incidence in the AO group. The results of logistic regression analysis showed that the relative risk of developing HT in individuals with AO was 2.33 (p=0.017; 95% confidence interval [CI], 1.17–4.63) and that the risk per 1-cm increase in WC from 1994 to 2002 was 1.06 (p=0.003; 95% CI, 1.02–1.10), both adjusted for several confounding factors. The results of this study suggest that, to prevent HT in Japanese, it is important to manage abdominal obesity and to monitor WC in individuals with or without abdominal obesity. (*Hypertens Res* 2008; 31: 1385–1390)

***Key Words*: abdominal obesity, hypertension, waist circumference, metabolic syndrome, community-based survey**

Introduction

In 2005, the Japanese Society of Internal Medicine and eight related scientific societies jointly announced new Japanese diagnostic criteria for the metabolic syndrome (MetS) (*1*). The new criteria include abdominal obesity as defined by waist circumference (WC).

The Ministry of Health, Labour and Welfare started a new program of health examinations in Japan in April 2008 (Health Service Bureau, Ministry of Health, Labour and Welfare: Standard program of medical examination and health guidance (fixed version). http://www.mhlw.go.jp/bunya/kenkou/seikatsu/index.html [accessed February 7, 2008; in Japanese]). This program adopts the Japanese diagnostic criteria for MetS in order to identify individuals at high risk for lifestyle-related and atherosclerotic diseases. Although the WC criterion will also be used to identify high-risk individuals in the new system, the usefulness of the criterion's definition of abdominal obesity as a predictor of hypertension (HT) is not known.

In this study, we investigated the incidence of HT in resi-

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dents of two rural communities in Japan to determine the relationship between HT and abdominal obesity.

Methods

Of the 1,525 residents who were aged 30 years or older when they received medical examinations in the towns of Tanno and Sobetsu, Hokkaido, in 1994, 712 also underwent medical examinations in 2002. We excluded the following individuals from those 712 residents: 14 individuals without data on blood pressure (BP) or WC, 140 individuals who were defined as having HT (systolic BP [SBP]≥140 mmHg and/or diastolic BP [DBP]≥90 mmHg) without medication, 146 individuals who were on medication for HT, and 16 individuals who had received medical treatment for coronary heart disease or cerebral vascular disease. The remaining 396 individuals were participants in this analysis. We received written informed consent from all participants.

WC, body mass index (BMI), SBP, DBP, fasting plasma glucose (FPG), total cholesterol (T.chol), triglyceride (TG), and HDL cholesterol (HDL-C) were measured in each subject. Blood samples were collected early every morning when the subjects felt hungry, at least 10 h after they had last eaten.

Participants with abdominal obesity were determined according to the new Japanese diagnostic criteria for MetS (*1*). Abdominal obesity is defined as WC≥85 cm for men and ≥90 cm for women.

The participants were divided into two groups: an abdominal obesity (AO) group and a non-AO group. The measured items were compared between the groups. We also compared the incidence of HT between the groups for subjects who were newly determined as having HT (subjects with SBP≥140 mmHg and/or DBP≥90 mmHg or subjects who were on medication for HT) on the basis of the 2002 medical examination data. Moreover, we estimated and compared the relative risk of developing HT between the groups.

SPSS Ver.12.0J (SPSS, Chicago, USA) was used for statistical analysis. All numerical values are expressed as means±SD. The unpaired *t*-test and the χ^2 test were used for the examination of intergroup differences and for frequency comparison, respectively. Multiple logistic regression analysis was used to estimate the relative risk of HT. The relative risk was adjusted for age, sex, and high-normal BP (SBP≥130 mmHg and/or DBP≥85 mmHg) in 1994, smoking (yes/no), FPG, and T.chol. In the same model, we assessed the effect of an increase in WC on the development of HT by using ΔWC (=WC [cm] in 2002 − WC [cm] in 1994). The significance level in all analyses was set at $p<0.05$.

This study was approved by the Ethics Committee of Sapporo Medical University.

Results

Table 1 shows the characteristics of the subjects in the non-AO and AO groups in 1994. Age, percentage of men, BMI, SBP, DBP, TC, TG, and FPG were higher in the AO group than in the non-AO group. HDL-C was significantly lower in the AO group than in the non-AO group.

Table 1. Basal Characteristics in the Non-AO Group and the AO Group in 1994

	Non-AO group (n=312)	AO group (n=84)
Age	57.2±9.3	59.5±8.8*
Men/women	112/200	75/9#
BMI (kg/m²)	22.4±2.3	25.5±3.0*
SBP (mmHg)	121.3±10.5	126.3±9.5*
DBP (mmHg)	73.5±6.9	77.4±6.6*
T.chol (mg/dL)	188.4±30.1	193.8±29.0*
TG (mg/dL)	110.1±68.5	159.8±82.1*
HDL-C (mg/dL)	58.1±13.8	48.6±12.2*
FPG (mg/dL)	92.1±11.7	105.1±27.8*

Age, percentage of men, BMI, SBP, DBP, TC, TG, and FPG were higher in the AO group than in the non-AO group. HDL-C was significantly lower in the AO group than in the non-AO group. *$p<0.05$, unpaired *t*-test, #$p<0.05$ χ^2 test. AO, abdominal obesity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T.chol, total cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; FPG, fasting plasma glucose.

In the 1994 data, there are significant positive correlations between WC and SBP and between WC and DBP in both men and women. There are also significant positive correlations between WC in 1994 and SBP in 2002 and between WC in 1994 and DBP in 2002 in both men and women (Fig. 1).

Figure 2 shows the percentage of HT in 2002 in each 1994 WC category. The higher the WC category, the higher the incidence of HT in both men and women. *p* for the trend was significant in both men and women.

The results of 10–11 years of follow-up are shown in Fig. 3. There were 312 individuals in the non-AO group and 84 in the AO group. Of the 312 individuals in the non-AO group, 177 remained in the non-AO category in 2002, but the remaining 79 individuals were changed to the AO category in 2002. Sixty-nine of the 84 individuals in the AO group remained in the AO category in 2002, but the remaining 15 individuals changed to the non-AO category. We divided the participants into these four groups (non-AO to non-AO, non-AO to AO, AO to non-AO and AO to AO) and compared the incidence of HT among them.

Figure 4 shows the incidences of HT in the four groups. The incidence was higher in the non-AO to AO group than in the non-AO to non-AO group (45.6% *vs.* 31.8%, $p=0.019$). It was also higher in the AO to AO group than in the AO to non-AO group (58.0% *vs.* 26.7%, $p=0.027$). There was no significant difference in the incidence of HT between the non-AO to non-AO group and the AO to non-AO group ($p=0.782$), or between the non-AO to AO group and the AO

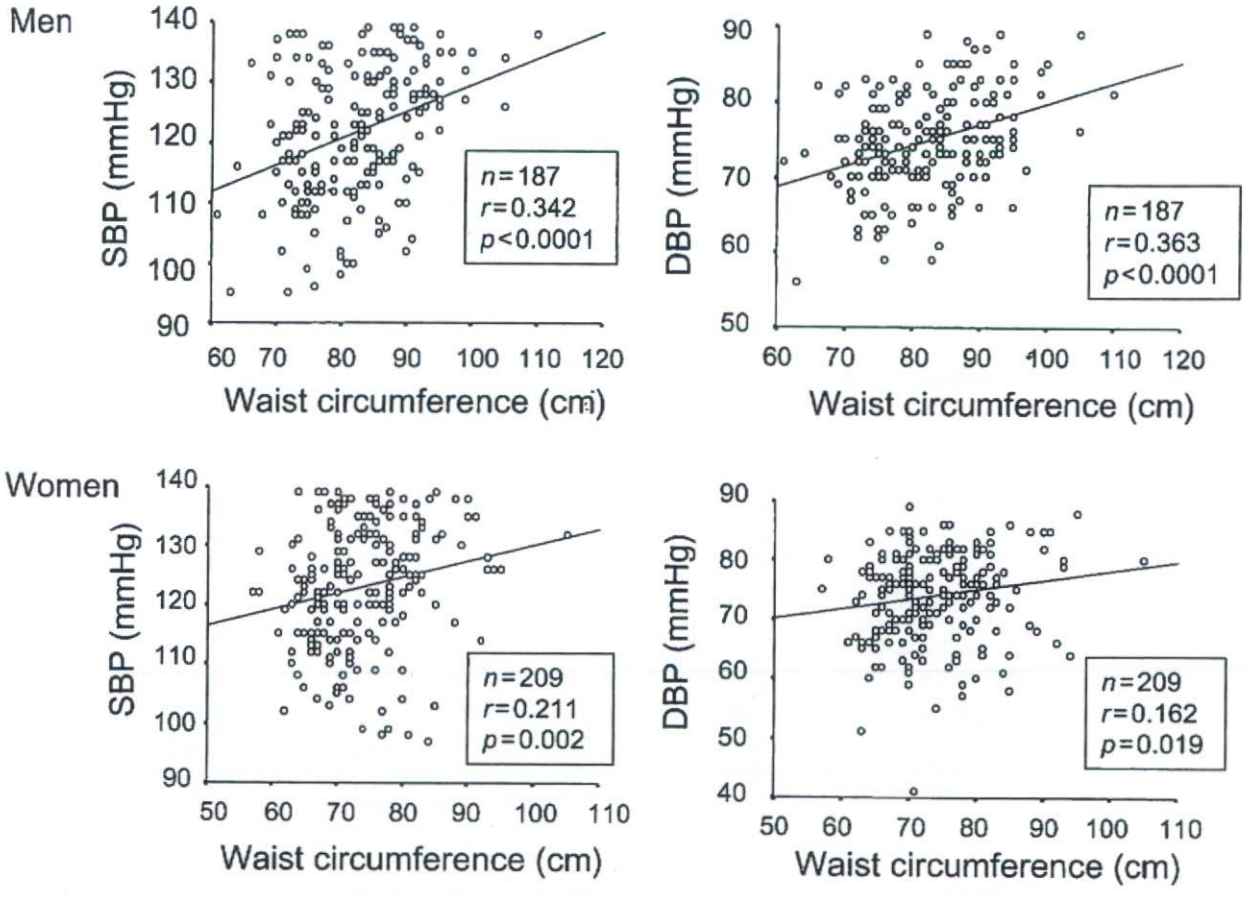

Fig. 1. *Correlations of waist circumference in 1994 with SBP and DBP in 2002. Upper: for men; lower: for women. Graphs on the left are relationships between waist circumference and SBP, and graphs on the right are relationships between waist circumference and DBP. Waist circumference shows significant positive correlations with SBP and DBP in both men and women.*

to AO group (p=0.142).

Table 2 shows the results of multiple logistic regression analysis. The relative risk of developing HT in individuals with AO was 2.33 (p=0.016; 95% confidence interval [CI], 1.17–4.63), and the risk per 1-cm increase in WC from 1994 to 2002 was 1.06 (p=0.003; 95% CI, 1.02–1.10), both adjusted for age, sex, high-normal BP in 1994, smoking (yes/no), FPG, and T.chol. When we additionally adjusted for BMI≥25 (yes/no) in the logistic regression model, the significance of AO disappeared (data not shown).

Discussion

The main findings of this study are 1) the incidence of HT was higher in the AO group than in the non-AO group, 2) increased WC, which may indicate the accumulation of visceral fat, increased the incidence of HT, 3) AO assessed by WC was significantly related to the development of HT (relative risk of HT: 2.33), 4) increasing WC was significantly related to the development of HT after adjustment for 1994 AO.

The Japanese Society of Internal Medicine and eight related scientific societies in Japan jointly announced new Japanese diagnostic criteria for MetS in April 2005 (*1*). According to the new criteria, the definition of MetS must include abdominal obesity, because the accumulation of visceral fat in individuals with MetS is considered to be important for the mechanism underlying the accumulation of risk factors for cardiovascular disease. Accumulation of visceral fat leads to insulin resistance and disorder of adipocytokines, and these factors in turn lead to high BP *via* mechanisms such as an increase in reabsorption of sodium in the renal tubule, hyperactivity of the sympathetic nervous system, proliferation of vascular smooth muscle cells and development of atherosclerosis. The results of this study show that abdominal obesity is significantly related to the development of HT and that an increase in WC, which may indicate the accumulation of visceral fat, is a risk factor for the development of HT.

It is well known that obesity is significantly related to HT, and many reports show relationships between BP levels and

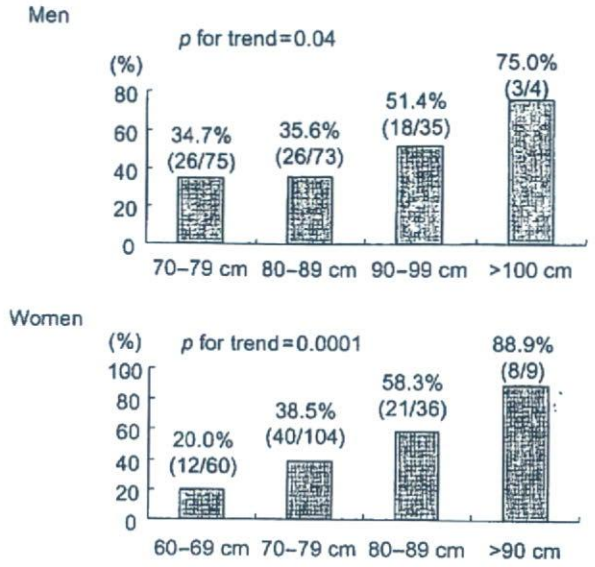

Fig. 2. *Percentage of hypertension (HT) in 2002 in each 1994 waist circumference (WC) category. The higher the WC category, the higher the incidence of HT in both men and women. p for the trend is significant in both men and women.*

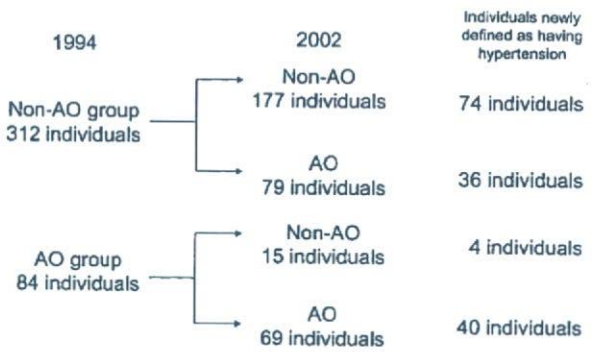

Fig. 3. *Follow-up results. There were 312 individuals in the non-AO group and 84 in the AO group. Of the 312 individuals in the non-AO group, 177 remained in the non-AO category in 2002, but the remaining 79 individuals changed to the AO category in 2002. Sixty-nine of the 84 individuals in the AO group remained in the AO category in 2002, but the remaining 15 individuals changed to the non-AO category in 2002. AO, abdominal obesity. Hypertension (HT): SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or receiving medication for HT.*

various anthropometric parameters (*2–12*). We also have reported a strong correlation between obesity assessed by BMI and the development of HT according to our cohort data (*13*), as well as a correlation between ultrasound-assessed visceral fat accumulation and BP levels (*14*).

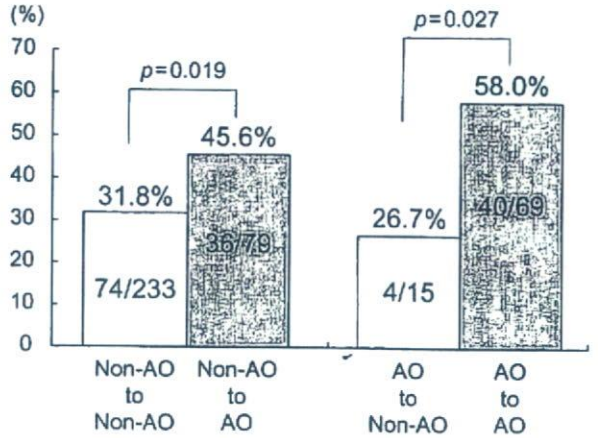

Fig. 4. *Incidences of hypertension (HT) in participants in the four groups. The incidence of HT is higher in the non-AO to AO group than in the non-AO to non-AO group (45.6% vs. 31.8%, p=0.019). The incidence of HT is also higher in the AO to AO group than in the AO to non-AO group (58.0% vs. 26.7%, p=0.027). There is no significant difference in the incidence of HT between the non-AO to non-AO group and the AO to non-AO group (p=0.782), or between the non-AO to AO group and the AO to AO group (p=0.142). AO, abdominal obesity.*

It is also known that a reduction in body weight leads to a decrease in BP levels (*15–20*). In the present study, no significant difference was found between the incidences of HT in the non-AO to non-AO group and the AO to non-AO group. Although this study was not interventional, the results suggest that weight reduction is effective for the prevention of HT. These results suggest that, to prevent hypertension, lifestyle modification is important for individuals with AO as well as for individuals with high-normal BP.

There are grounds for controversy about the current Japanese cutoff points for abdominal obesity (85 cm for men and 90 cm for women). The International Diabetes Federation (IDF) recommends that Asian cutoff points (90 cm for men and 80 cm for women) should be used for diagnosing MetS in Japanese people (The IDF consensus worldwide definition of the metabolic syndrome. http://www.idf.org/webdata/docs/MetS_def_update2006.pdf [accessed February 7, 2008]). In the present study, the prevalence of abdominal obesity was significantly lower in women than in men. According to Fig. 1, the incidence of HT in women increased continuously with the increase of WC. We tried to plot the receiver operator characteristic (ROC) curves for WC to predict the development of HT in men and women separately. The areas under the curves were 0.560 for men and 0.684 for women. According to the ROC curves, the cutoff levels yielding the maximal sensitivity plus specificity for predicting the development of