nary restenosis after PCI.

Lipid profile did not differ between the recurrence group and the non-recurrence group except for TC, which was significantly lower in the recurrence group, presumably because of the strict control of TC level in the subjects during their hospitalization. The proportion of subjects taking cholesterol-lowering drugs was approximately 50% in both groups.

Study Limitations

This study has 3 limitations. First, subjects were hospitalized at least once, and in many of the cases, CAD was severe. Second, the number of subjects was relatively small. Further investigation using a larger number of subjects is necessary to confirm the present observation. The third limitation concerns recurrence. In this study, the recurrence group of subjects was defined as those who had been diagnosed as having CAD during their first admission and who had been discharged after receiving PCI, CABG and drug therapy and then had chest pain because of ischemia, which was confirmed by results of exercise tolerance tests, nuclear medical examinations and imaging examinations carried out regularly on an outpatient basis, during their second admission. The methods used for diagnosis and the treatment methods differed among the subjects, and the criteria for diagnosis of recurrence were not uniform. However, data for all of the subjects included in the recurrence group were used for analysis because exclusion of subjects not strictly meeting the criteria would have resulted in a very small number of subjects. It is also possible that the mechanisms of restenosis and new stenosis of the coronary artery are different, and the risk factors for new stenosis might not always be involved in restenosis. However, in this study, there were few cases of confirmed new stenosis, and some of the cases of confirmed new stenosis also included restenosis. It has also been reported that the rate of restenosis is high in cases of CAD complicated with DM. In this study, we therefore did not differentiate restenosis and new stenosis in our analysis of the effects of risk factors on stenosis.

In conclusion, our study revealed that CAD progresses at the stage of abnormal glucose tolerance and that the rate of ischemic episode recurrence increases in individuals with abnormal glucose tolerance, DM and HT. Therefore, it is important to manage and control glucose tolerance, IR and blood pressure for prevention of CAD.

References

1. Sekikawa A, Eguchi H, Tominaga M, Igarashi K, Abe T, Manaka H, et al. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in a rural area of Japan: The Funagata diabetes study. *J Diabetes Complications* 2000; **4:** 78–83.
2. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: The Hisayama Study. *Diabetologia* 1993; **36:** 1198–1203.
3. Nakano M, Saitoh S, Takagi S, Fujisawa J, Aoyama S, Shimamoto K, et al. Prevalence of glucose intolerance in Japan: From the National Circulatory Disorders Basic Survey, 1990. *Nippon Ronen Igakkai Zasshi* 1998; **35:** 839–844.
4. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339:** 229–234.
5. Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. *Arch Intern Med* 2004; **164:** 1438–1443.
6. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al. Impact of diabetes on mortality after the first myocardial infarction: The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998; **21:** 69–75.
7. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women: The Framingham Study. *JAMA* 1988; **260:** 3456–3460.
8. Takagi S, Saitoh S, Shimamoto K. Long-term prognosis for diabetics in general population of two rural communities in Japan: A prospective eighteen-year follow-up study. *J Jpn Diabetes Society* 1998; **41:** 257–265.
9. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: The Funagata Diabetes Study. *Diabetes Care* 1999; **22:** 920–924.
10. Deirdre B, James M, Denis M, Samer N, Reubin A, David N, et al. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased level of coronary heart disease risk factors. *Diabetes* 2004; **53:** 2095–2100.
11. Qing Q, Johan E, Pekka J, Jaakko T. Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care* 2003; **26:** 2910–2914.
12. Kataoka Y, Yasuda S, Morii I, Otsuka Y, Kawamura A, Miyazaki S. Quantitative coronary angiographic studies of patients with angina pectoris and impaired glucose tolerance. *Diabetes Care* 2005; **28:** 2217–2222.
13. Horimoto M, Hasegawa A, Ozaki T, Takenaka T, Igarashi K, Inoue H. Independent predictors of the severity of angiographic coronary atherosclerosis: The lack of association between impaired glucose tolerance and stenosis severity. *Atherosclerosis* 2005; **182:** 113–119.
14. Austen WG, Edwards JE, Frye RL, Gensini GC, Gott VL, Grifith LSC, et al. AHA Committee Report: A reporting system on patients evaluated for coronary artery disease: Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; **51:** 5–40.
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
16. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20:** 1183–1197.
17. Oimatsu H, Saitoh S, Ura N, Shimamoto K. A practical index for evaluation of insulin resistance. *J Jpn Diabetes Society* 2000; **43:** 205–213.
18. Dortimer AC, Shenoy PN, Shiroff RA, Leaman DM, Babb JD, Liedtke AJ, et al. Diffuse coronary artery disease in diabetic patients: Fact or fiction? *Circulation* 1978; **57:** 133–136.
19. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients: The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996; **94:** 1818–1825.
20. Satoh H, Terada H, Uehara A, Katoh H, Matsunaga M, Yamazaki K, et al. Post challenge hyperinsulinaemia rather than hyperglycemia is associated with the severity of coronary artery disease in patients without a previous diagnosis of diabetes mellitus. *Heart* 2005; **91:** 731–736.
21. Takezako T, Saku K, Zhang B, Shirai K, Arakawa K. Insulin resistance and angiographical characteristics of coronary atherosclerosis. *Jpn Circ J* 1999; **63:** 666–673.
22. Fujiwara T, Saitoh S, Takeuchi H, Isobe T, Miura T, Shimamoto K, et al. Development and progression of atherosclerotic disease in relation to insulin resistance and hyperinsulinemia. *Hypertens Res* 2005; **28:** 665–670.
23. Kwon K, Choi D, Koo BK, Ryu SK. Decreased insulin sensitivity is associated with the extent of coronary artery disease in patients with angina. *Diabetes Obes Metab* 2005; **7:** 579–585.
24. Hikita N, Tuchihashi K, Nakata T, Ura N, Shimamoto K. Involvement of glucose metabolism abnormalities and insulin resistance in atherosclerotic coronary artery disease: Semiquantitative coronary angiography study. *J Cardiol* 1998; **32:** 291–300.
25. Nemes A, Lengyel C, Forster T, Varkonyi TT, Takacs R, Nagy I, et al. Coronary flow reserve, insulin resistance and blood pressure response to standing in patients with normoglycaemia: Is there a relationship? *Diabet Med* 2005; **22:** 1614–1618.
26. Zhang XF, Attia J, D'este K, Yu XH, Wu XG. Prevalence and magnitude of classical risk factors for coronary heart disease in a cohort

of 4400 Chinese steelworkers over 13.5 years follow-up. *Eur J Cardiovasc Prev Rehabil* 2004; **11:** 113–120.
27. Mora S, Yanek LR, Moy TF, Fallin MD, Becker LC, Becker DM, et al. Interaction of body mass index and framingham risk score in predicting incident coronary disease in families. *Circulation* 2005; **111:** 1871–1876.
28. Nasir K, Campbell CY, Santos RD, Roguin A, Braunstein JB, Carvalho JA. The association of subclinical coronary atherosclerosis with abdominal and total obesity in asymptomatic men. *Prev Cardiol* 2005; **8:** 143–148.
29. Nishio K, Fukui T, Tsunoda F, Kawamura K, Itoh S, Konno N, et al. Insulin resistance as a predictor for restenosis after coronary stenting. *Int J Cardiol* 2005; **103:** 128–134.

Original Article

Effects of Hypertension and Type 2 Diabetes Mellitus on the Risk of Total Cardiovascular Events in Japanese Patients with Hypercholesterolemia: Implications from the Japan Lipid Intervention Trial (J-LIT)

Kazuaki SHIMAMOTO[1], Toru KITA[2], Hiroshi MABUCHI[3], Masunori MATSUZAKI[4], Yuji MATSUZAWA[5], Noriaki NAKAYA[6], Shinichi OIKAWA[7], Yasushi SAITO[8], Jun SASAKI[9], and Hiroshige ITAKURA[10], the J-LIT Study Group

Hyperlipidemia, hypertension, and diabetes mellitus (DM) are well-established risk factors for cardiovascular disease. We analyzed the cardiovascular events in hyperlipidemic patients with or without DM who were administered open-labeled simvastatin in groups stratified by blood pressure level using data from the Japan Lipid Intervention Trial (J-LIT). Hyperlipidemic patients with DM (n=6,288) had significantly more cardiovascular events than those without DM (n=33,933). The incidence rates of total cardiovascular events in the Non-DM and DM groups were 15.40 and 25.76 per 1,000 patients for the 6-year period, respectively. The relative risk of total cardiovascular events in the DM *vs.* the Non-DM group was 1.68, and the relative risk was significantly higher in the DM than in the Non-DM group. The relative risks of total cardiovascular events were significantly higher in DM and Non-DM patients whose systolic blood pressure (SBP) was greater than or equal to 130 mmHg compared to that of Non-DM patients whose SBP was less than 130 mmHg, and in DM and Non-DM patients whose diastolic blood pressure (DBP) was greater than or equal to 80 mmHg compared to that of Non-DM patients whose DBP was less than 80 mmHg. In all groups stratified by SBP and DBP, relative risks of total cardiovascular events were higher in DM patients than in Non-DM patients. For patients with hypercholesterolemia and DM, blood pressure should be strictly controlled in order to prevent both coronary events and stroke. These results are in good agreement with the JNC 7 and the ESH/ESC guidelines for DM patients, which recommended that the SBP and DBP be less than 130 and 80 mmHg, respectively. (*Hypertens Res* 2007; 30: 119–123)

***Key Words*: hyperlipidemia, diabetes mellitus, hypertension, simvastatin, cardiovascular events**

From the [1]Sapporo Medical University School of Medicine, Sapporo, Japan; [2]Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]Kanazawa University Graduate School of Medicine, Kanazawa, Japan; [4]Yamaguchi University Graduate School of Medicine, Ube, Japan; [5]Sumitomo Hospital, Osaka, Japan; [6]Nakaya Clinic, Tokyo, Japan; [7]Nippon Medical School, Tokyo, Japan; [8]Chiba University Graduate School of Medicine, Chiba, Japan; [9]International University of Health and Welfare Graduate School, Fukuoka, Japan; and [10]Ibaraki Christian University, Hitachi, Japan.

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Address for Reprints: Kazuaki Shimamoto, M.D., Sapporo Medical University School of Medicine, 16 Minamiichijo Nishi, Chuo-ku, Sapporo 060-0061, Japan. E-mail: simamoto@sapmed.ac.jp

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Introduction

Cardiovascular and cerebrovascular complications are the leading causes of death and disability in patients with diabetes mellitus (DM) (*1*, *2*). DM is associated with a marked increase (by a factor of two to four) in the risk of coronary heart disease (CHD) (*3*). Prospective epidemiological studies have confirmed DM as an independent risk factor of stroke with an increased relative risk ranging from 2-fold to 5-fold (*2*). Fujishima *et al.* (*4*) reported that DM was a significant risk factor for both CHD and stroke in Japanese people. Many epidemiological studies have demonstrated that lowering blood pressure reduced the risk of coronary events and stroke (*5–8*). According to both the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6) and the World Health Organization–International Society of Hypertension (WHO-ISH) 1999 report (*9*, *10*), the recommended systolic blood pressure (SBP) and diastolic blood pressure (DBP) in DM patients were 130 and 85 mmHg, respectively. In the Hypertension Optimal Treatment (HOT) Study (*11*), the risk of major cardiovascular events in DM patients whose DBP was greater than or equal to 80 mmHg was found to be one-half of the risk in DM patients whose DBP was greater than or equal to 90 mmHg. In the UK Prospective Diabetes Study (UKPDS), tight blood pressure control in patients with hypertension and type 2 diabetes improved both cardiovascular disease and diabetes-related outcomes (*12*). In step with these results, the recommended SBP/DBP in DM patients have been changed to 130/80 mmHg in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (*13*).

The Japan Lipid Intervention Trial (J-LIT) study was the first and largest nationwide cohort study involving more than 50,000 hypercholesterolemic patients under the conditions of ordinary clinical practice to evaluate the relationship between lipid levels and the incidence of CHD (*14–17*) or cerebrovascular disease (*18*). Using the J-LIT database, we examined the relationship between the incidence of cardiovascular events and both blood pressure level and target blood pressure level in DM patients stratified by SBP and DBP.

Methods

Subject

The J-LIT study enrolled 52,421 patients with serum total cholesterol (TC) levels of ≥220 mg/dl: men aged 35 to 70 years and postmenopausal women under 70 years old between 1992 and 1993. When the patients had been treated with lipid-lowering agents, they were screened for eligibility after a washout period of at least 4 weeks; the washout lasted for at least 12 weeks in patients previously treated with probucol. The exclusion criteria included a recent coronary event or stroke, uncontrolled DM, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any other illness with a poor prognosis. Patients without documented CHD and without any history of coronary intervention or stroke at the time of enrollment were analyzed in this report.

Treatment and Endpoints

The design of the J-LIT study has been described previously (*14*). Patients were treated with open-labeled simvastatin at a dose of 5 to 10 mg/day. All patients were monitored for 6 years from 1993 to June 1999. Their lipid levels, adverse events, coronary events and stroke were documented in the medical records. No restrictions were placed on the medical treatment for complications. Sitting blood pressure was measured using a sphygmomanometer. Body weight, blood pressure, and the fasting serum lipid levels were measured every 6 months after enrollment and patients were interviewed about drug compliance, number of cigarettes smoked, alcohol consumption, and amount of exercise. Every 12 months, hepatic and renal functions were monitored, and an electrocardiogram test was performed. DM was diagnosed as a fasting blood glucose level of ≥126 mg/dl (*19*).

The primary endpoints of the present analysis were coronary events (myocardial infarction and sudden cardiac death) and stroke. All coronary events and stroke that occurred during the study period were evaluated by the Endpoint Classification Committee. Each patient was informed of the study purpose, as well as the drug efficacy and the need for long-term treatment. Written informed consent was not obtained from the patients, because commercially available simvastatin preparations were used for this open-labeled study.

Statistical Analysis

All data, including those obtained after the termination of simvastatin therapy, were analyzed by survival analysis. The mean blood pressure was calculated using the data obtained throughout the study period. The mean TC level was calculated using the same data set excluding the baseline values. The values of blood pressure and TC level after the onset of any disease (including the primary endpoints) were excluded from the present analysis. For the analysis of baseline patient age and lipid profiles, continuous variables within and between subgroups were assessed using the paired or unpaired *t*-test or the analysis of variance using a trend test. Patients were classified into 4 and 5 subgroups based on the mean DBP and SBP levels, respectively. The reference values were taken as the mean from subjects in the Non-DM subgroup exhibiting the lowest blood pressure. We calculated the relative risks using 95% confidence intervals (CI) for each endpoint of each subgroup relative to the reference value; for this analysis, the Cox proportional-hazards model was used with adjustments for gender and age at baseline (as a continu-

ous variable), smoking habit and drinking habit (as a categorized data). The data are expressed as the mean±SD. For all of the statistical analyses, a p value of <0.05 was considered to be significant. All statistical calculations were performed using the SAS software package (version 8.02; SAS Institute Inc., Cary, USA).

Results

Characteristics of the Study Patients

The characteristics of the patients' backgrounds are shown in Table 1. Among the 40,221 patients screened for this analysis, 6,288 (15.6%) hypercholesterolemic patients had type 2 diabetes as well. The ratio of males to females in the DM group was higher than that in the Non-DM group. The rates of drinkers and smokers in the DM group were higher than those in the Non-DM group. Fasting blood glucose levels in the DM group were significantly higher than those in the Non-DM group. Serum triglyceride levels in the DM group were higher than those in the Non-DM group, but not significantly so. Other lipid parameters were not different between the DM and Non-DM groups. TC levels during the study period in DM and Non-DM patients were 218.5±31.3 and 220.8±29.1 mg/dl, respectively. SBP and DBP at baseline in Non-DM patients were 139.1±18.9 and 82.2±11.3 mmHg, respectively; and the corresponding values for DM patients were 140.6±18.8 and 81.6±11.0 mmHg, respectively. No remarkable changes in SBP or DBP were observed during the entire study period.

Table 1. Baseline Characteristics of the Subjects, Risk Factors, Lipid and Blood Pressure Profiles

	Non-DM (n=33,933)	DM (n=6,288)
Male (%)	29.7	39.7
Age (years old)	57.7±7.9	57.8±7.8
BMI (kg/m^2)	23.9±3.1	24.4±3.4
Hypertension (%)	63.1	66.4
ECG abnormality* (%)	12.3	15.0
CHD familial history (%)	4.8	4.6
Smoking habit (%)	15.6	21.2
Drinking habit (%)	28.0	33.9
Lipid		
TC (mg/dl)	269.8±34.4	270.1±34.7
LDL-C (mg/dl)	182.7±33.6	181.0±32.9
TG (mg/dl)	189.1±156.2	226.9±222.7
HDL-C (mg/dl)	53.3±15.0	51.3±15.3
FBG (mg/dl)	95.6±21.1	153.8±56.1
Blood pressure		
SBP (mmHg)	139.1±18.9	140.6±18.8
DBP (mmHg)	82.2±11.3	81.6±11.0

BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Study physician's diagnosis.

Incidence of Cardiovascular Events

The crude incidence of coronary events in Non-DM and DM has been already reported (*17*). The adjusted incidence of coronary events and/or stroke was analyzed in the Non-DM and DM groups and the results are shown in Table 2. The incidence rates of coronary events in the Non-DM and DM groups were 3.50 and 7.39, and those of stroke were 11.85 and 18.10 per 1,000 patients for the 6-year period, respectively. The respective incidence rates of coronary events and stroke in the DM group were higher than those in the Non-DM group. The incidence rates of total cardiovascular events in the Non-DM and DM groups were 15.40 and 25.76 per 1,000 patients for the 6-year period, respectively. The respective relative risks of coronary events, stroke and total cardiovascular events in the DM *vs.* the Non-DM group were 2.12 (95% CI, 1.55 to 2.89), 1.53 (95% CI, 1.25 to 1.88) and 1.68 (95% CI, 1.42 to 2.00).

Relationships between the Relative Risk of Total Cardiovascular Events and Blood Pressure during the Study Period

The relative risk of total cardiovascular events was significantly higher in DM and Non-DM patients whose SBP was greater than or equal to 130 mmHg compared to that of Non-DM patients with SBP of less than 130 mmHg. The relative risk was significantly higher in DM and Non-DM patients whose DBP was greater than or equal to 80 mmHg compared to that of Non-DM patients with DBP of less than 80 mmHg (Fig. 1). However, in all groups stratified by SBP and DBP, relative risks of total cardiovascular events were higher in DM patients than those in Non-DM.

Discussion

The J-LIT study was the first and largest epidemiological study in Japan to demonstrate a relationship between serum lipid levels and the incidence of CHD or total mortality in Japanese patients with hypercholesterolemia (*16*). Since the J-LIT study was conducted under a common clinical environment in a target population of hypercholesterolemic patients throughout the country, the findings could be reasonably extrapolated to the general Japanese hypercholesterolemic population. The J-LIT study was thought to be a good model system to elucidate the influence of having multiple risk factors on the cardiovascular events. Although the J-LIT study enrolled hypercholesterolemic patients, the results could be used for epidemiological purposes, because lipid levels were well controlled in many patients throughout the study period

Table 2. Adjusted Incidence* of Coronary Events and Stroke during the Treatment Periods

	Non-DM (n=33,933)		DM (n=6,288)		p value
	Number of events	Incidence rate	Number of events	Incidence rate	
Coronary events	131	3.50	57	7.39	<0.001
Stroke	405	11.85	121	18.10	<0.001
Total cardiovascular events	536	15.40	178	25.76	<0.001

Coronary events: acute myocardial infarction and sudden cardiac death. Total cardiovascular events: coronary events and stroke. Incidence rate: number of incidence per 1,000 patients for the 6 years period. DM, diabetes mellitus.*Adjusted for age, gender, hypertension, total cholesterol, smoking habit and drinking habit.

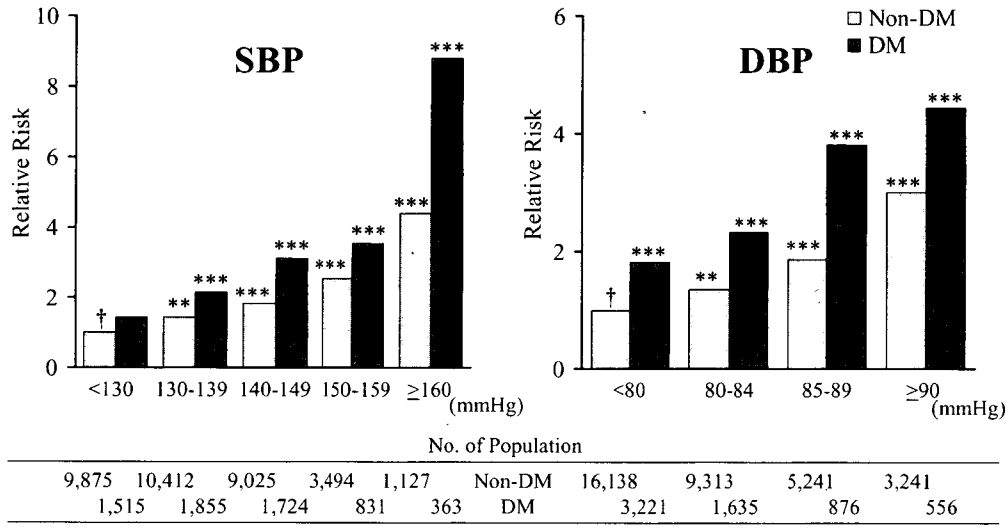

Fig. 1. *Relationships between the relative risk of total cardiovascular events and blood pressure during the study period. †Data in the groups of non-diabetic patients with SBP <130 mmHg and DBP <80 mmHg were used as reference values.* **p<0.01, ***p<0.001 vs. *the reference values. All data were adjusted for gender, age, total cholesterol, smoking habit, and drinking habit.*

and the results were adjusted using TC levels.

In our previous study (*16*), we reported that the serum TC and low-density lipoprotein cholesterol levels were positively correlated and the serum high-density lipoprotein cholesterol level was inversely correlated with the risk of CHD in patients without a history of CHD. We have also reported that the risk of total cardiovascular events increased at lower blood pressure level in the group with poorer lipid control than in the well-controlled group, and concluded that blood pressure should be strictly controlled for the prevention of both coronary events and stroke in addition to lowering the serum TC level in patients with hypercholesterolemia and hypertension (*20*). It should be considered that the outcomes of this study were limited, because all patients were treated with simvastatin, which has pleiotropic effects. The blood pressure level posing a significant risk might be lower in patients without statin treatment than in the patients studied here.

In the present study, we analyzed the effects of hypertension and DM on the risk of cardiovascular events using the J-LIT data. The relative risk of total cardiovascular events in the DM *vs.* the Non-DM group was 1.68, and the risk was significantly higher in the DM group. In all groups stratified by SBP or DBP, the relative risks of total cardiovascular events were higher in DM than in Non-DM patients. The risk was significantly higher in both DM and Non-DM patients whose SBP was greater than or equal to 130 mmHg compared to the risk in Non-DM patients whose SBP was less than 130 mmHg. The risk increased significantly in Non-DM patients with DBP greater than or equal to 80 mmHg. When DBP was even less than 80 mmHg, the risk in DM patients was significantly higher than in Non-DM patients. It was suggested that the target SBP/DBP levels were less than 130/80 mmHg in Japanese hypertensive patients with DM. These findings were in good agreement with the JNC 7 (*13*) and American Diabetes Association (*21*) and ESH/ESC (*22*) guidelines for DM patients, which recommended that the target SBP/DBP be less than 130/80 mmHg.

For patients with hypercholesterolemia and DM, blood pressure should be strictly controlled to help prevent both coronary events and stroke.

References

1. Howard BV, Rodrigues BL, Bennett PH, *et al*: Diabetes and cardiovascular disease: Writing Group I: epidemiology. *Circulation* 2002; **105**: e132–e137.
2. Goldstein LB, Adams R, Becker K, *et al*: Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation* 2001; **103**: 163–182.
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16**: 434–444.
4. Fujishima M, Kiyohara Y, Kato I, *et al*: Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* 1996; **45**: S14–S16.
5. Kannel WB, McGee D, Gordon T: A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol* 1976; **38**: 46–51.
6. Stamler J, Stamler R, Neaton JD: Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med* 1993; **153**: 598–615.
7. Stegmayr B, Asplund K, Kuulasmaa K, Rajakangas AM, Thorvaldsen P, Tuomilehto J: Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA Project: an ecological study of 18 populations. *Stroke* 1997; **28**: 1367–1374.
8. He J, Whelton PK: Elevated systolic blood pressure and risk of cardiovascular and renal disease: overview of evidence from observational epidemiologic studies and randomized controlled trials. *Am Heart J* 1999; **138**: 211–219.
9. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
10. Guidelines Sub-Committee: 1999 World Health Organization–International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999; **17**: 151–183.
11. Hansson L, Zanchetti A, Carruther SG, *et al*, HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; **351**: 1755–1762.
12. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703–713.
13. Chobanian AV, Bakris GL, Black HR, *et al*: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
14. Matsuzawa Y, Itakura H, Kita T, *et al*: Design and baseline characteristics of a cohort study in Japanese patients with hypercholesterolemia: the Japan Lipid Intervention Trial (J-LIT). *Curr Ther Res* 2000; **61**: 219–243.
15. Matsuzawa Y, Kita T, Mabuchi H, *et al*: Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients. *Circ J* 2003; **67**: 287–294.
16. Matsuzaki M, Kita T, Mabuchi H, *et al*: Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. *Circ J* 2002; **66**: 1087–1095.
17. Oikawa S, Kita T, Mabuchi H, *et al*: Risk of coronary events in Japanese patients with both hypercholesterolemia and type 2 diabetes mellitus on low-dose simvastatin therapy: implication from Japan Lipid Intervention Trial (J-LIT). *Atherosclerosis* 2007 (in press, online available).
18. Nakaya N, Kita T, Mabuchi H, *et al*: Large-scale cohort study on the relationship between serum lipid concentrations and risk of cerebrovascular disease under low-dose simvastatin in Japanese patients with hypercholesterolemia: sub-analysis of the Japan Lipid Intervention Trial (J-LIT). *Circ J* 2005; **69**: 1016–1021.
19. Kuzuya T, Nakagawa S, Satoh J, *et al*: Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Jpn Diab Soc* 1999; **42**: 385–404.
20. Shimamoto K, Kita T, Mabuchi H, *et al*: The risk of cardiovascular events in Japanese hypertensive patients with hypercholesterolemia: sub-analysis of the Japan Lipid Intervention Trial (J-LIT) study, a large-scale observational cohort study. *Hypertens Res* 2005; **28**: 879–887.
21. Arauz-Pacheco C, Parrott MA, Raskin P: Hypertension management in adults with diabetes. *Diabetes Care* 2004; **27**: S65–S67.
22. European Society of Hypertension–European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.

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Risk of coronary events in Japanese patients with both hypercholesterolemia and type 2 diabetes mellitus on low-dose simvastatin therapy: Implication from Japan Lipid Intervention Trial (J-LIT)

Shinichi Oikawa[a,*], Toru Kita[b], Hiroshi Mabuchi[c], Masunori Matsuzaki[d], Yuji Matsuzawa[e], Noriaki Nakaya[f], Yasushi Saito[g], Jun Sasaki[h], Kazuaki Shimamoto[i], Hiroshige Itakura[j],

The J-LIT Study Group

[a] *Nippon Medical School, Tokyo, Japan*
[b] *Kyoto University Graduate School of Medicine, Kyoto, Japan*
[c] *Kanazawa University Graduate School of Medicine, Kanazawa, Japan*
[d] *Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan*
[e] *Sumitomo Hospital, Osaka, Japan*
[f] *Nakaya Clinic, Tokyo, Japan*
[g] *Chiba University Graduate School of Medicine, Chiba, Japan*
[h] *International University of Health and Welfare Graduate School, Fukuoka, Japan*
[i] *Sapporo Medical University School of Medicine, Hokkaido, Japan*
[j] *Ibaraki Christian University, Ibaraki, Japan*

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Abstract

Hypercholesterolemic patients with type 2 diabetes mellitus are at increased risk of coronary heart disease (CHD); however, direct evidence is very limited in Japanese patients. The J-LIT is the first nationwide study conducted to assess the relationship between serum lipid levels and development of coronary events in Japanese hypercholesterolemic patients. We analyzed the coronary events in the J-LIT study subjects by having type 2 diabetes or not. Of the total 41,801 subjects without prior CHD who received open-label simvastatin, 5 mg/day, 6554 (male 40.2%, age 57.8 ± 7.8) subjects had type 2 diabetes, while 35,247 (male 30.0%, age 57.8 ± 7.9) did not.

In this analysis, relative coronary event risks based on a 0.26 mmol/l (10 mg/dl) increase in low density lipoprotein-cholesterol (LDL-C), were similar between hypercholesterolemic subjects with and without type 2 diabetes (17.3% versus 19.4%). Although all subjects were treated with simvastatin, the subjects with type 2 diabetes have significantly more coronary events compared to the subjects without type 2 diabetes (1.80/1000 and 0.76/1000 patient-years, respectively). Given the results above, to reduce the risk of coronary events in Japanese patients with both hypercholesterolemia and type 2 diabetes, careful and strict cholesterol management is needed in addition to the control of blood glucose.

Keywords: J-LIT; Hypercholesterolemia; Type 2 diabetes; Coronary disease; Myocardial infarction; Simvastatin; Cohort study

* Corresponding author. Tel.: +81 3 3822 2131x7207/5802 8153; fax: +81 3 5802 8153.
E-mail address: shinichi@nms.ac.jp (S. Oikawa).

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Hypercholesterolemia is a significant risk factor for coronary heart disease (CHD) [1–4], and the risk of CHD-related events is five to seven times higher in patients with atherosclerotic diseases than subjects without them. Therefore, reducing the total cholesterol (TC) level is critical for the patients with atherosclerotic diseases [5,6]. In the previous reports [7,8], we demonstrated the clear relationship between low density lipoprotein-cholesterol (LDL-C) levels and CHD risk in the Japanese subjects. Lifestyle factors, such as diet and exercise, have strong influences on the risk of CHD development. While the incidence of CHD in Japan is still much lower than that in western countries [9,10], TC levels in Japanese people have been increasing, probably due to the westernized lifestyles (e.g., increased intake of animal fats and proteins) [11,12], which might subsequently increase the incidence of CHD. The westernized lifestyle might also be one of the major reasons that type 2 diabetes mellitus, has also been increasing dramatically over the past 20–30 years in Japan [13]. Type 2 diabetes is also well-established as a risk factor for the development of CHD.

Many investigators in the western countries have reported that patients with both hypercholesterolemia and type 2 diabetes have more increased risk for the incidence of coronary events (acute myocardial infarction and sudden cardiac death) compared to patients with hypercholesterolemia alone (reviewed in Ref. [14]). However, there is no data on this issue in Japan based on a large scale epidemiological survey. Therefore, it is worthwhile to analyze the J-LIT (Japan Lipid Intervention Trial) study for this purpose. The J-LIT was the first nationwide observational cohort study in Japan with a large number of hypercholesterolemic patients treated in usual clinical practice, and it was designed to assess the relationship between the lipid levels and the incidence of CHD [15]. In Japan, cholesterol lowering therapy is well established; therefore placebo control group was not placed for ethical and practical reasons. J-LIT patients without prior CHD (myocardial infarction or angina pectoris) were classified into diabetic and non-diabetic groups and we analyzed the incidence of coronary events and coronary deaths. We also assessed the relationship between the incidence of coronary events and risk factors in the study period.

1. Research design and methods

The design of the J-LIT study was described previously [15]. The study involved 6500 general practitioners throughout the country and enrolled 52,421 patients including men aged 35–70 years and postmenopausal women under 70 years of age, with a TC level $\geq$5.69 mmol/l. Exclusion criteria were recent acute myocardial infarction (MI) or stroke within a month, uncontrolled diabetes mellitus, serious concomitant hepatic or renal disease, secondary hypercholesterolemia, malignancy or any illness with poor prognosis. Patients were selected throughout Japan and received open-label simvastatin, 5–10 mg/day. The dosing was decided according to the approved Japanese labeling of Lipovas®. Lipid levels, adverse events, and coronary events were monitored for 6 years. Another lipid-lowering agent was permitted to use when serum TC level did not show an adequate response to simvastatin monotherapy 10 mg/day.

The primary endpoints were coronary events, including acute MI and sudden cardiac death. All coronary events during the study period were assessed by the Endpoint Classification Committee. Each patient was informed of the study purpose, as well as drug efficacy and the need of long-term treatment. In this report, we used criteria for the diagnosis of type 2 diabetes established in 1999 by the Japan Diabetes Society (JDS), which are similar to the WHO type 2 diabetes diagnostic criteria.

1.1. Statistical analysis

All data were analyzed using survival analysis. For baseline patient characteristics, patients were classified into groups with and without type 2 diabetes. The average lipid levels were calculated using the data obtained throughout the study period. In the cases of the subjects who experienced any other diseases or coronary events after the enrollment of the study, the lipid data after the events were excluded from the calculation. For the risk of CHD events, patients were stratified according to average lipid levels (TC, LDL-C, TG, and HDL-C) during the treatment period. TC, LDL-C, TG and HDL-C were classified into discrete intervals of 0.52, 0.52, 0.56 and 0.26 mmol/l, respectively. Reference categories were set for the subgroups of the lowest lipid levels. Relative risks with 95% confidence intervals were calculated using the Cox proportional-hazard model [16] with adjustment for baseline characteristics (gender, age, hypertension, type 2 diabetes mellitus, fasting blood glucose, and smoking). For all statistical analysis, p values < 0.05 were considered significant. All statistical calculations were performed using SAS software (version 6.12, SAS Institute Inc., Cary, NC).

2. Result

2.1. Follow-up of subjects

Of the 52,421 patients enrolled in the J-LIT study, 47,294 patients were screened for the primary prevention cohort study [7]. In this investigation, data collected from 41,801 of the patients were used for analysis; 5493 patients were excluded for the following reasons: lack of follow-up data (932 patients), violation of inclusion criteria (63 patients), unwillingness to participate (6 patients), and incomplete data on covariates (4492 patients). In the 6 years from the date of enrollment, 31,370 patients were followed up by the investigators. The average length of follow-up was 5.39 years per subject.

Table 1
Baseline characteristics and lipid profiles of the subjects by diabetes status

	DM	Non-DM	p-Value
Number of patients	6554	35247	
Male gender (%)	40.2	30.0	<0.001
Age (years)	57.8 ± 7.8	57.8 ± 7.9	0.536
Obesity (%)[a]	39.5	32.5	<0.001
Hypertension (%)	46.1	45.9	0.691
ECG abnormality (%)	15.1	12.5	<0.001
Family history of CHD (%)	4.5	4.8	0.317
Smoking habit (%)	21.3	15.6	<0.001
Alcohol consumption (%)	33.9	28.0	<0.001
Exercise (%)	59.1	48.8	<0.001
Fasting blood glucose (mmol/l)	8.53 ± 3.12	5.31 ± 1.16	<0.001
Lipid profiles			
Baseline (mmol/l)			
TC	6.98 ± 0.90	6.97 ± 0.88	0.353
LDL-C	4.68 ± 0.85	4.72 ± 0.87	<0.001
HDL-C	1.32 ± 0.40	1.38 ± 0.39	<0.001
TG	2.56 ± 2.51	2.14 ± 1.76	<0.001

During treatment (mmol/l)		% Change		% Change	
TC	5.64 ± 0.81	−19.2	5.70 ± 0.75	−18.2	<.001
LDL-C	3.38 ± 0.76	−27.8	3.47 ± 0.75	−26.5	<.001
HDL-C	1.39 ± 0.35	+5.3	1.44 ± 0.35	+4.3	<.001
TG	2.04 ± 1.46	−20.3	1.81 ± 1.07	−15.4	<.001

DM, type 2 diabetes; ECG, electrocardiogram; CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol, TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol. Data are mean ± S.D.
[a] Obesity, body mass index ≥ 25 kg/m^2.

2.2. Baseline characteristics of the study patients

Of the 41,801 patients included in this analysis, 6554 (15.7%) had type 2 diabetes. The baseline characteristics of the patients with and without type 2 diabetes mellitus are shown in Table 1. There are characteristic differences between the patients with and without type 2 diabetes. Proportions of male, and obesity, were higher in the patients with type 2 diabetes mellitus ($p < 0.001$). Also, the rate of performing casual exercise was higher in the patients with type 2 diabetes, probably because they had been encouraged taking exercise by physicians due to their high blood glucose.

In patients with type 2 diabetes mellitus, oral hypoglycemic agents were used in 40.5%, while insulin was used in 5.6% of them.

2.3. Lipid levels

Table 1 illustrates the lipid levels at baseline and during the treatment period in the diabetic and non-diabetic patients. As shown, the lipid levels were similar between the two groups except TG ($p < 0.001$). This suggests that simvastatin is effective for the treatment of hypercholesterolemia, in both patient groups.

2.4. Incidence of coronary events

A total of 207 coronary events occurred during the study period (Table 2). As predicted, the incidence rate of coronary events is markedly higher in the hypercholesterolemic patients with type 2 diabetes than in the subjects without

Table 2
Incidence of coronary events

	N (incidence rate)		Relative risk (95% CI)	p-Value
	DM	Non-DM		
Coronary events	62 (1.80)	145 (0.76)	2.38 (1.77–3.21)	<0.001
			2.11 (1.56–2.85)	<0.001[a]
Fatal	25 (0.73)	37 (0.19)	3.75 (2.26–6.22)	<0.001
			3.31 (1.98–5.51)	<0.001[a]
Non-fatal	37 (1.07)	108 (0.57)	1.91 (1.32–2.78)	<0.001
			1.70 (1.17–2.47)	0.006[a]

DM, type 2 diabetes; incidence rate/1000 patient-years; CI, confidence interval.
[a] Adjusted with age, sex.

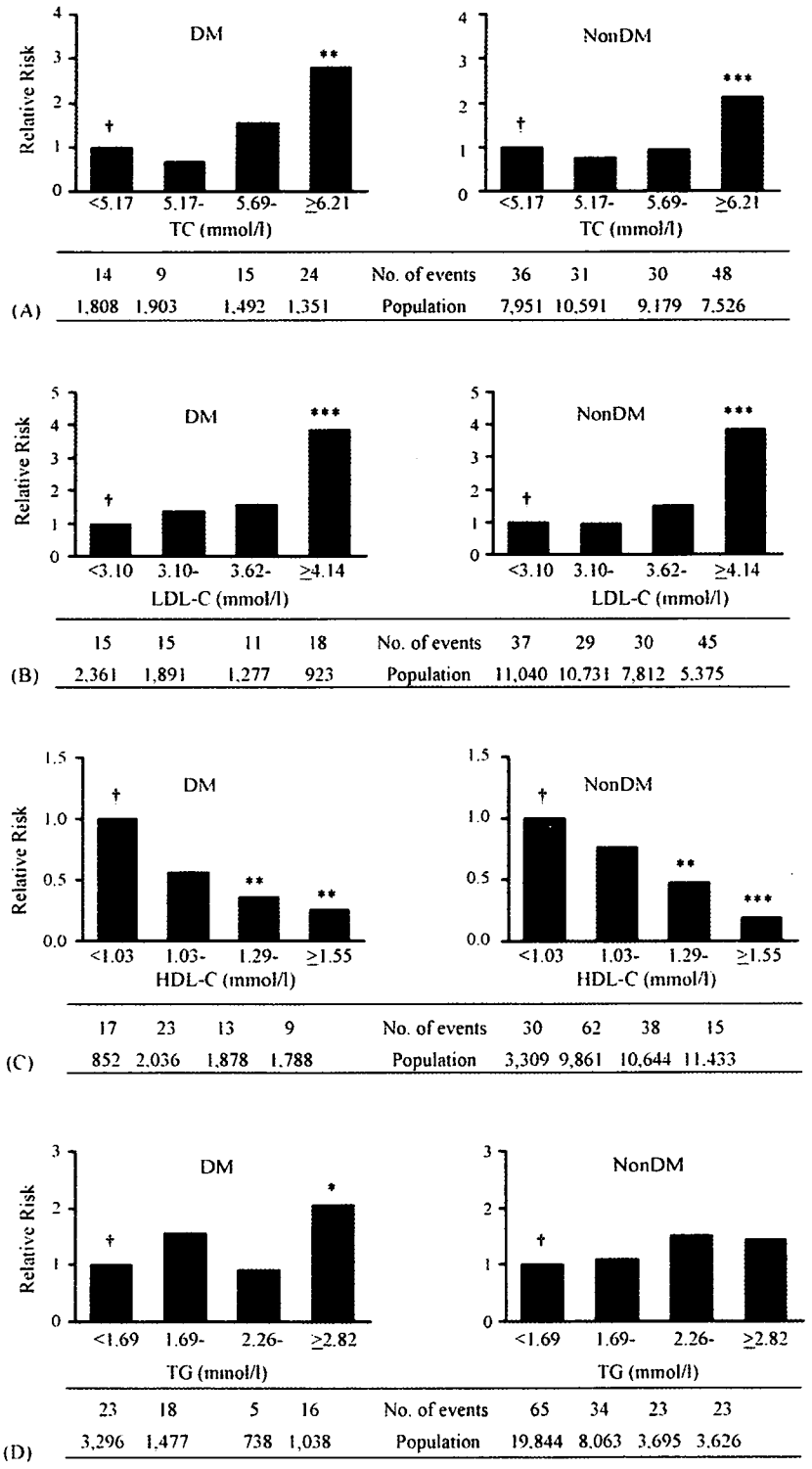

Fig. 1. Relative risk of coronary events based on lipid total cholesterol (TC) (A), low density lipoprotein-cholesterol (LDL-C) (B), high density lipoprotein-cholesterol (HDL-C) (C) and triglycerides (TG) (D) levels during treatment for patients with and without diabetes. Coronary events: myocardial infarction and sudden cardiac death. DM, type 2 diabetes. Adjusted with sex, age, hypertension, fasting blood glucose, and smoking habit.

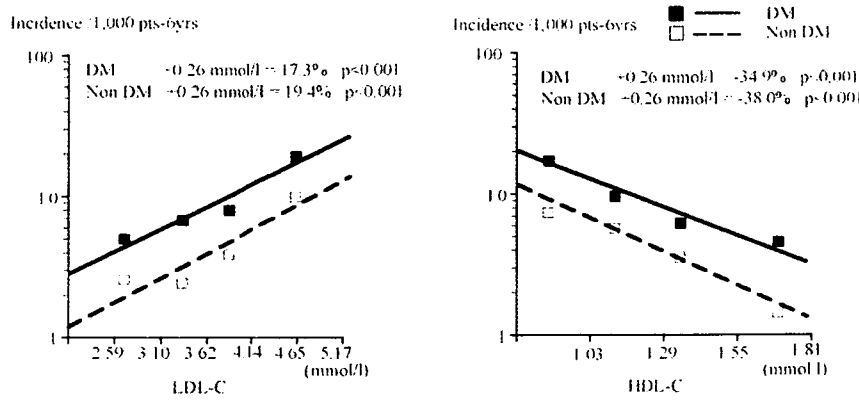

Fig. 2. The incidence of coronary events and lipid levels during treatment. Coronary events: myocardial infarction and sudden cardiac death. DM, type 2 diabetes. Adjusted with sex, age, hypertension, fasting blood glucose, and smoking habit.

it (1.8/1000 patient-years versus 0.76/1000 patient-years), despite ongoing treatment for type 2 diabetes during the study period. The relative risk of coronary event for type 2 diabetes was 2.38 (95% confidence interval 1.77–3.21, $p<0.001$), and age and sex adjusted risk was 2.11 (95% CI 1.56–2.85, $p<0.001$).

2.5. Relative risk of coronary events based on lipid levels during the treatment

Patients in both groups were stratified in four groups based on TC levels. Fig. 1(A) illustrates that the subgroups with TC levels higher than 6.21 mmol/l have significantly higher risk of coronary events in the both subjects with and without type 2 diabetes compared to those with TC < 5.17 mmol/l ($p=0.003$ with type 2 diabetes and $p<0.001$ without type 2 diabetes).

Patients in both groups were stratified in four groups based on LDL-C levels. Fig. 1(B) illustrates that the subgroups with LDL-C levels higher than 4.14 mmol/l have significantly higher risk of coronary events in the both groups with and without type 2 diabetes compared to those with LDL-C < 3.10 mmol/l ($p<0.001$ in both groups).

Patients in both groups were stratified in four groups based on HDL-C levels. Fig. 1(C) illustrates that the subgroups with HDL-C levels higher than 1.29 mmol/l have significantly lower risk of coronary events in the both subjects with and without type 2 diabetes compared to those with HDL-C < 1.03 mmol/l ($p=0.006$ and 0.003, respectively).

The relationship between the TG levels and coronary events risk is shown in Fig. 1(D). In patients without type 2 diabetes, the risk of coronary events does not differ based on TG level. On the other hand, in patients with type 2 diabetes, TG levels greater than 2.82 mmol/l showed two-fold increased risk of coronary events comparing to that of TG < 1.69 mmol/l ($p=0.033$).

2.6. Relationship between lipid levels and the incidence of coronary events

The incidence of coronary event at different levels of LDL-C and HDL-C are illustrated in Fig. 2. For subjects with and without type 2 diabetes, an increase of 0.26 mmol/l (10 mg/dl) in LDL-C is associated with a 17.3 and 19.4% increase, respectively, in the risk of coronary events. On the other hand, an increase of 0.26 mmol/l (10 mg/dl) in HDL-C is associated with a 34.9% ($p<0.001$) and 38.0% ($p<0.001$) decrease, respectively, in the risk of coronary events. The association with an increase of 0.11 mmol/l (10 mg/dl) in TG and the risk of coronary events is weak (1.3%, $p=0.051$ in type 2 diabetes and 1.2%, $p=0.051$ in non-diabetes, respectively).

2.7. Relative risk of coronary events by baseline characteristics

The relative risks of coronary events analyzed by the patients' baseline characteristics are shown in Fig. 3. Male patients with hypercholesterolemia generally have more

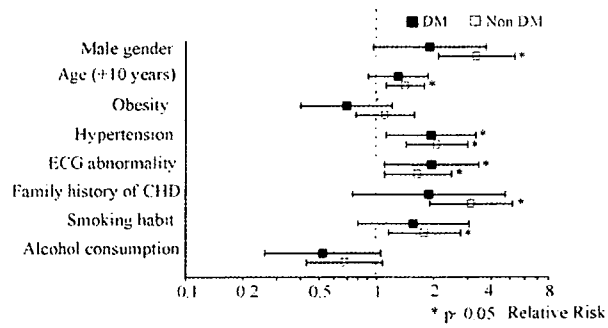

Fig. 3. Relative risk of coronary events by baseline characteristics. Coronary events: myocardial infarction and sudden cardiac death. Obesity, body mass index ≥ 25 kg/m^2; DM, type 2 diabetes. Adjusted with sex, age, hypertension, electrocardiogram abnormality, family history of CHD, smoking habit, and alcohol consumption.

increased risk for CHD development than female hypercholesterolemic patients. However, our result clearly revealed that for the patients with both hypercholesterolemia and type 2 diabetes, the gender difference in the risk for coronary events becomes smaller (3.33, $p<0.001$–1.94, $p=0.057$). The patients' baseline characteristics, such as hypertension ($p=0.017$ with type 2 diabetes and $p<0.001$ without type 2 diabetes), electrocardiogram abnormality ($p=0.024$ and 0.009, respectively), family history of CHD ($p=0.170$ and $p<0.001$, respectively) and smoking habit ($p=0.200$ and 0.006, respectively) increase the risk for coronary events as expected.

On the other hand, our analysis showed that alcohol consumption had tendency to reduce the risk of coronary events for hypercholesterolemic patients with or without type 2 diabetes, although it was not statistically significant ($p=0.072$ and 0.105, respectively). However, it should be noted that the subjects who consumed alcohol in the current study were *light-moderate* drinkers, (approximate average was 38 g ethanol/day), thus this influence of alcohol consumption on the coronary events might be limited to that level and may differ from heavy drinkers without diabetes.

Also, obesity did not appear to be a risk factor of coronary events for both hypercholesterolemic patients with and without type 2 diabetes in this analysis ($p=0.187$ and 0.510, respectively). (The reason of this result is explained in Section 3.).

The risk of coronary event for oral hypoglycemic agents 1.78 (95% CI 1.04–3.03, $p=0.036$), insulin 5.35 (95% CI 2.65–10.81, $p<0.001$).

In this study, 1136 hypercholesterolemic patients had slightly high fasting blood glucose level (6.11–6.99 mmol/l), and 11 of these subjects developed coronary events in the study period. We calculated the relative risk of developing a coronary events for the hypercholesterolemic subjects with slightly high fasting blood glucose level compared to those with hypercholesterolemia alone (adjusted with age, sex, hypertension and smoking). The relative risks was 2.11 (95% CI 1.14–3.91, $p=0.017$).

3. Discussions

The J-LIT, a long-term prospective cohort study on the use of simvastatin, is the first epidemiological study in Japan to demonstrate the relationship between serum lipid levels and the incidence of CHD in Japanese patients with hypercholesterolemia [17]. The J-LIT study provides excellent data to elucidate the coronary event risk associated with having both hypercholesterolemia and type 2 diabetes.

Since the J-LIT study was conducted in a standard clinical environment in a target population of hypercholesterolemic patients throughout the country, the findings could be reasonably extrapolated to the general Japanese population. The study monitored hypercholesterolemic patients treated with low-dose simvastatin (5–10 mg/day) over 6 years. Of the 41,801 subjects, 6554 patients (15.7%) had type 2 diabetes as well. This morbidity was lower than that of the US study which reported 25% of hypercholesterolemic study patients had type 2 diabetes [18]. The traditional Japanese diet, constituted mainly of vegetables, carbohydrate and low protein, may contribute to the lower morbidity of type 2 diabetes, although the younger generations' diet has become steadily westernized.

We have already reported that serum TC and LDL-C levels were positively correlated and serum HDL-C level was inversely correlated with the risk of CHD in the hypercholesterolemic patients without a history of CHD in the J-LIT study [7]. In the present investigation, the same pattern of risk for coronary events can be seen in both hypercholesterolemic patients with and without type 2 diabetes. For the patients with type 2 diabetes, the relative risk was higher (2.06, 95% CI 1.06–4.02, $p=0.033$) in 2.82 mmol/l for TG. We further analyzed the adjusted relative risks for LDL-C or HDL-C. After that, the risks for TG adjusted with LDL-C did not change, while the risk for TG disappeared (1.33, 95% CI 0.66–2.68, $p=0.432$) after the adjustment with HDL-C. We observed that HDL-C was confounding factor for the risk of TG for coronary events.

This study demonstrated that hypercholesterolemic patients with slightly high fasting blood glucose level have the same level of increased risk for coronary events as hypercholesterolemic subjects with typical type 2 diabetes. Although the fasting blood glucose level was not matched high to the diabetes mellitus, such patients should be managed as strictly as the same as the patients with type 2 diabetes and hypercholesterolemia. Early management for glucose control, including diet and exercise are necessary when the fasting blood glucose level were between 6.11 and 6.99 mmol/l in order to prevent later serious outcomes.

We also found that alcohol intake at low to moderate levels may reduce the risk of coronary events in patients with hypercholesterolemia, with and without type 2 diabetes. In Japan, for patients with lifestyle-associated diseases, such as hyperlipidemia and type 2 diabetes, alcohol intake has been thought to accelerate the progression of CHD. Thus alcohol consumption is sometimes even prohibited by the physicians in these patients. However, based on this large scale J-LIT study results, further consideration should be given to the role of alcohol consumption at different levels.

Obesity has been considered as a risk factor of type 2 diabetes and CHD. In this study, obesity was not shown as a risk factor. The standard diagnosis criteria for the metabolic syndrome revised lately, adopts the waist circumference for defining obesity (male: >85 cm, female: >90 cm). It was not observed that obesity was an independent risk factor in the present study. It might be caused by that BMI instead of waist circumference was utilized in this. This report based on the J-LIT study, for the first time, clearly reveals that the Japanese hypercholesterolemic patients with type 2 dia-

betes have higher risk for developing coronary events. Thus, Japanese patients with both risk factors need more careful and strict management of LDL-C, HDL-C and TG in addition to the blood glucose control for the prevention of coronary events.

4. Limitation

This study is post hoc non-randomized, observational subanalysis.

Acknowledgment

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References

[1] National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel II). Circulation 1994;89:1333–445.
[2] Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986;256:2835–8.
[3] Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986;256:2823–8.
[4] Keys A, Menotti A, Aravanis C, et al. The Seven Countries Study 2,289 deaths in 15 years. Prev Med 1984;2:141–54.
[5] Pedersen TR, et al. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
[6] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
[7] Matsuzaki M, et al. A large scale cohort study on the relationship between serum cholesterol levels and coronary events in Japanese patients with hypercholesterolemia: Japan Lipid Intervention Trial (J-LIT)—primary prevention study. Circ J 2002;66:1087–95.
[8] Horiuchi H, et al. Primary cardiovascular events and serum lipid levels in elderly Japanese with hypercholesterolemia under 6-year simvastatin treatment: a sub-analysis of the J-LIT Study. J Am Geriatr Soc 2004;52:1981–7.
[9] Kodama K, Sasaki H, Shimizu Y. Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up. Hiroshima/Nagasaki study. Jpn Circ J 1990;54:414–21.
[10] Wakugami K, Iseki K, Kimura Y, et al. Relationship between serum cholesterol and the risk of acute myocardial infarction in a screened cohort in Okinawa, Japan. Jpn Circ J 1998;62:7–14.
[11] Okayama A, Ueshima H, Marmot MG, et al. Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan 1980–1989. Int J Epidemiol 1993;22:1038–47.
[12] Investigating Committee on Guidelines for Diagnosis Treatment of Hyperlipidemias Japan, Atherosclerosis Society. Guidelines for diagnosis and treatment of hyperlipidemias in adults. Jpn J Atheroscler 1997;25:1–34.
[13] Kawamori R. Diabetes trends in Japan. Diabetes Metab Res Rev 2002;18:S9–S13.
[14] Gotto AM. Lipid management in diabetic patients: lessons from prevention trials. Am J Med 2002;112(Suppl 8A):19S–26S.
[15] Matsuzawa Y, Itakura H, Kita T, et al. Design and baseline characteristics of a cohort study in Japanese patients with hypercholesterolemia: The Japan Lipid Intervention Trial (J-LIT). Curr Therapeu Res 2000;61:219–43.
[16] Cox DR. Regression models and life tables (with discussion). J R Stat Soc 1972;B34:187–220.
[17] Matsuzawa Y, et al. Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients: implication of the J-LIT study, a large scale nationwide cohort study. Circ J 2003;67:287–94.
[18] Rubins HB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. N Engl J Med 1999;341:410–8.

Original Article

Visceral Obesity in Japanese Patients with Metabolic Syndrome: Reappraisal of Diagnostic Criteria by CT Scan

Mariko EGUCHI[1)], Kazufumi TSUCHIHASHI[1)], Shigeyuki SAITOH[1)], Yoshihiro ODAWARA[2)], Tohru HIRANO[2)], Tomoaki NAKATA[1)], Tetsuji MIURA[1)], Nobuyuki URA[1)], Masato HAREYAMA[2)], and Kazuaki SHIMAMOTO[1)]

To reappraise the cutoff level of abdominal circumference (AC) for diagnosis of visceral obesity in Japanese, we examined the association of visceral fat deposition with other constituents of metabolic syndrome and atherosclerotic cardiovascular disease (ASCD). CT was used for determination of visceral-fat area (VFA), subcutaneous-fat area (SFA) and AC on CT (AC_{CT}) in 420 Japanese patients with (n=180) or without ASCD (n=240). VFA cutoff levels were calculated by receiver operating characteristic (ROC) analysis. AC_{CT} correlated with VFA (r=0.828), SFA (r=0.795), and AC measured with an anthropometric tape (AC_M, r=0.96). The VFA cutoff levels yielding the maximum sensitivity and specificity to predict two or more components of metabolic syndrome were 92 cm^2 in males and 63 cm^2 in females, which correspond to AC_M values of 83 cm and 78 cm, respectively. The male AC_M cutoff level was similar to the AC in current Japanese criteria (85 cm), but the female AC_M cutoff level was considerably smaller than the criteria, and this change in cutoff level increased the prevalence of metabolic syndrome in females three-fold. The cutoff levels of VFA for predicting presence of ASCD were 98 cm^2 in males and 75 cm^2 in females, corresponding to AC_M values of 84 cm and 80 cm, respectively. The present results obtained by CT support the validity of the current Japanese criteria for visceral obesity in males but not in females. AC_M of 78 cm appears to be a cutoff level suitable for diagnosing visceral obesity in Japanese females, though further confirmation is needed. (*Hypertens Res* 2007; 30: 315–323)

***Key Words*: metabolic syndrome, coronary arterial disease, visceral obesity, aging**

Introduction

Clustering of major risk factors (hypertension, diabetes mellitus, and hyper-lipidemia) has been shown to have synergistic effects on the development of atherosclerotic cardiovascular disease (ASCD) (*1*, *2*). The contribution of clustered minor risk factors for ASCD has also received attention recently, and attractive clinical concepts (*3–6*) emerged in the 1980s: metabolic syndrome X, insulin resistance syndrome, visceral fat syndrome, and multiple risk factor syndrome. Currently, the cluster of minor metabolic factors for ASCD is referred to as metabolic syndrome, and consists of visceral obesity, glucose intolerance or insulin resistance, dyslipidemia, and raised blood pressure. However, several definitions of metabolic syndrome, which differ in their required combinations of risk factors and cutoff levels for each factor, have been proposed (*7–9*).

One of the marked differences among the current diagnostic criteria of metabolic syndrome is the method used to assess visceral obesity and its requirement for diagnosis. In the definition of metabolic syndrome by the National Choles-

From the [1)]Second Department of Internal Medicine and [2)]Department of Radiology, Sapporo Medical University School of Medicine, Sapporo, Japan.
Address for Reprints: Mariko Eguchi, M.D., Ph.D., Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060–0061, Japan. E-mail: eguchi@sapmed.ac.jp
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Table 1. Clinical Backgrounds in Studied Subjects

	All (n=420)	Male (n=235)	Female (n=185)
Age (years old)	62±15	63±14	61±17
Gender [male/female]	235/185		
Risk factors (n (%))			
Hypertension	275 (66)	163 (69)	112 (61)
Diabetes mellitis	141 (34)	84 (36)	57 (31)
Hyperlipidemia	297 (71)	167 (71)	130 (70)
Hyperuricemia	132 (32)	93 (40)	39 (21)*
Smoking	174 (42)	143 (63)	31 (17)*
Family history	65 (16)	34 (15)	31 (17)
Weight (kg)	60±14	65±14	53±11*
BMI (kg/m^2)	23±4	23±4	22±4*
Systolic blood pressure (mmHg)	134±21	135±20	133±20
Diastolic blood pressure (mmHg)	77±13	77±13	76±13
Major disease (n (%))			
Coronary heart disease	122 (29)	88 (37)	34 (18)
Cardiomyopathy	33 (8)	19 (8)	14 (8)
Valvular disease	40 (10)	15 (6)	25 (14)
Aortic disease	41 (10)	27 (11)	14 (8)
Arrhythmia	61 (15)	38 (16)	23 (12)
Renal disease	56 (13)	27 (11)	29 (16)
Stroke	12 (3)	7 (3)	5 (3)
Others	54 (17)	14 (6)	40 (22)
Medication (n (%))			
Antihypertensive agents	241 (57)	149 (63)	92 (50)*
Antihyperlipidemia agents	112 (26)	49 (21)	63 (34)*
Antidiabetic agents	81 (19)	45 (19)	36 (20)

All the variables are expressed as mean±1 SD. *p<0.05 *vs.* male group, respectively.

terol Education Program Adult Treatment Panel III (NCEP ATP III) (*7*), visceral obesity is not a requisite. However, visceral obesity needs to be present in metabolic syndrome as defined by the International Diabetes Federation (IDF 2005) (*8*) and the Examination Committee of Criteria for Metabolic Syndrome in Japan (Japanese criteria) (*9*). In these definitions, visceral obesity is assessed by abdominal (waist) circumference, but its cutoff level is not the same: abdominal circumferences (ACs) are ≥102 cm in males and ≥88 cm in females in the NCEP ATP III criteria, ≥85–94 cm in males and ≥80–90 cm in females, depending on ethnic groups, in the IDF criteria, and ≥85 cm in males or ≥90 cm in females in the Japanese criteria. These differences in diagnostic criteria of visceral obesity derive from different rationales in each subject population.

In the present study, we used multi-detector-row CT (MDCT) to reappraise visceral obesity criteria for the diagnosis of metabolic syndrome and screening of ASCD in Japanese subjects. Since visceral fat, but not subcutaneous fat, is primarily responsible for the production of cytokines relevant to the development of metabolic syndrome (*10*, *11*), the amounts of visceral and subcutaneous fat were separately determined by MDCT together with AC. The relationships between the amount of visceral fat and metabolic syndrome or ASCD were analyzed by use of receiver operating characteristic (ROC) curves, and the results suggest that the current Japanese criterion of visceral obesity in males (AC=85 cm) is valid but that the criterion for females needs to be modified possibly to AC of 78 cm.

Methods

Study Subjects

We enrolled 420 consecutive patients who underwent MDCT at Sapporo Medical University Hospital between January 2001 and December 2003 (Table 1). Informed consent for use of their data in scientific research was obtained from all study subjects. Data from each subject were saved in anonymous formats and securely stored in a computer. Information on coronary risk factors, including data on the blood pressure category, serum triglyceride and high-density lipoprotein (HDL) cholesterol levels and presence/absence of ASCD, was obtained by physical and laboratory examinations. Unless otherwise stated, metabolic syndrome was diagnosed in accordance with the current Japanese criteria (*10*), which

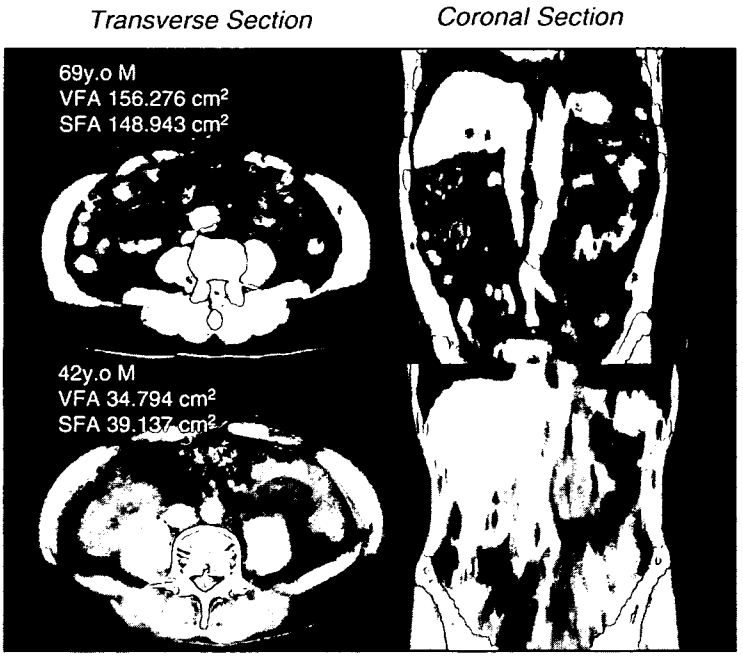

Fig. 1. *Representative MDCT images used for determination of visceral fat area and subcutaneous fat area. CT slices at the level of the umbilicus were used for the determination of areas. VFA, visceral fat area; SFA, subcutaneous fat area. Upper: a case of visceral obesity; Lower: a non-obese case.*

require the presence of visceral obesity (defined as a waist measurement of ≥85 cm in males or ≥90 cm in females) and two or more of the following minor abnormalities: 1) glucose intolerance (fasting blood glucose ≥110 mg/dl) or taking medication for diabetes, 2) serum triglyceride ≥150 mg/dl, 3) HDL cholesterol <40 mg/dl in either males and females, and 4) blood pressure ≥130/85 mmHg. Cases of severe congestive heart failure (NYHA IV), ascites, malignant tumor, thyroidal disease, and the other emaciating disorders were excluded from the study to prevent entry bias. General obesity was determined as body mass index (BMI) ≥25%, following the criteria of the Japanese Society of Obesity (*12*). ASCD in this study included coronary artery disease, cerebrovascular disease, arotic atherosclerotic disease, and atherosclerotic valvular heart disease. The subclinical forms of atherosclerosis, such as thickening of the intima in the carotid artery, were not examined and not included in ASCD in this study.

Determination of Visceral and Subcutaneous Fat Areas by MDCT

All of the MDCT images were obtained either by Aquillion 4DAS (Toshiba Inc., Tokyo, Japan) or Light Speed Ultra 8DAS (General Electrics Japan Co., Tokyo, Japan) with a minimal slice width of 5–7 mm. Data were stored on visual servers and retrospectively analyzed using commercially supplied software without information regarding patients' cardiovascular and biochemical parameters. The fat areas in each subject were determined from an image at the level of the umbilicus (Fig. 1) with Virtual Place (AZE Inc., Tokyo, Japan). Subcutaneous fat was defined as the extraperitoneal fat between skin and muscle, with attenuation ranging from −150 to −50 Hounsfield units. The intraperitoneal part with the same density as the subcutaneous fat layer was defined as visceral fat. The visceral fat area (VFA) and subcutaneous fat area (SFA) were determined by automatic planimetry.

Determination of AC

AC on CT (AC_{CT}) was determined in all subjects from CT images at the umbilical level using a mobile caliper. In 80 randomly selected subjects (37 males and 43 females), abdominal circumference (AC_M) was also measured with an anthropometric tape to confirm its correlation with AC_{CT}.

Statistical Analysis

All numeric variables are expressed as the means±SD. Differences in the incidences between groups were tested by the χ^2 test. Comparison of group mean data was performed by one-way analysis of variance (ANOVA) and Bonferroni's post hoc test. The correlation between two values was evaluated by linear and exponential regression analyses. Difference between regression lines was examined by analysis of covariance. Values of $p<0.05$ were considered statistically significant. ROC analysis was performed to determine cutoff

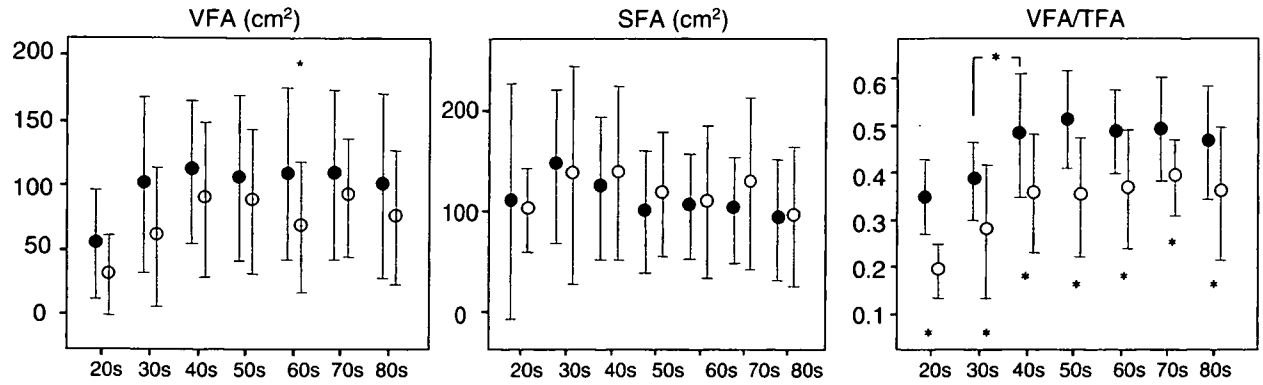

Fig. 2. *Age-related difference in the levels of visceral and subcutaneous fat accumulation. VFA, visceral fat area; SFA, subcutaneous fat area; VFA/TFA, ratio of VFA to total fat areas (VFA+SFA). Closed circles and open circles indicate the data for males and females, respectively.* *p < 0.05 vs. *males.*

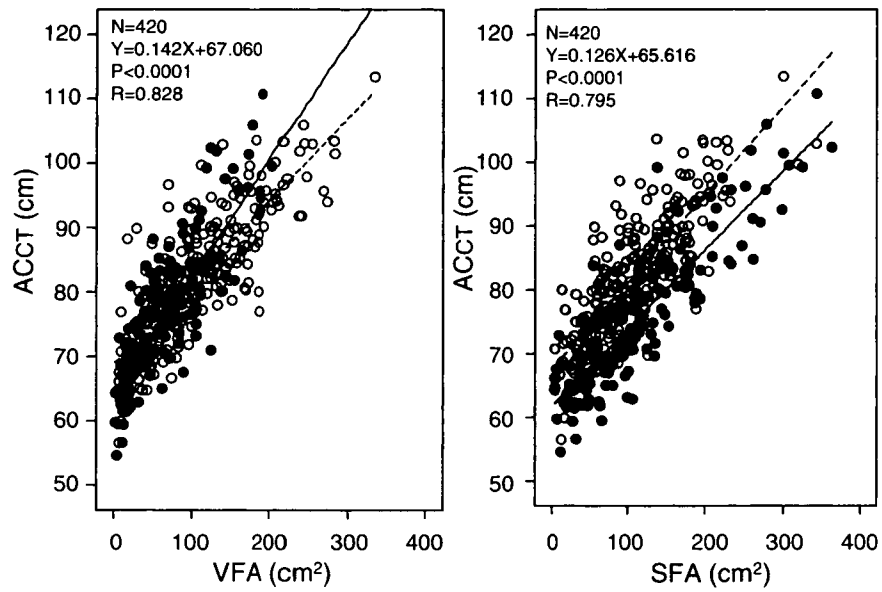

Fig. 3. *Correlation between abdominal circumference (AC_{CT}) and accumulation of visceral (VFA) and subcutaneous fat (SFA). Open circles and closed circles indicate the data for males and females, respectively. There was no significant difference in the regression lines for the AC_{CT}-VFA relationships between males (broken line) and females (solid line). However, the regression line for the AC_{CT}-SFA relationship was shifted upwards in females compared with males.*

points of VFA yielding the maximum sensitivity and specificity for predicting metabolic syndrome and ASCD.

Results

Characteristics of Subjects

As shown in Table 1, we enrolled 420 patients aged 62±15 years old (age range, 14–92 years). The age and incidences of risk factors, except for hyperuricemia and smoking, were comparable in the male and female subjects. Of the 420 patients, 180 (42.9%) had ASCD, and the incidence of coronary artery disease tended to be higher in males than in females, though the difference was not statistically significant. The percentages of subjects on pharmacological treatments for hypertension, hyperlipidemia and diabetes were 57%, 26% and 19%, respectively.

Visceral and Subcutaneous Fat Deposition in Age Subgroups

Figure 2 shows the levels of VFA and SFA and ratio of VFA to total fat area (TFA; TFA=VFA+SFA) in each age group. There was a trend for lower VFA and higher SFA in subjects

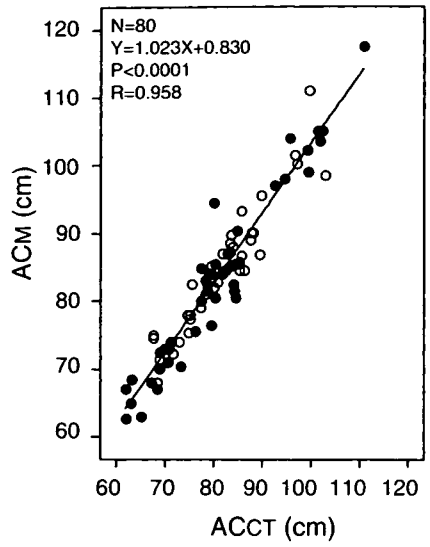

Fig. 4. *Correlation between MDCT-determined abdominal circumference (AC_{CT}) and abdominal circumference measured by anthropometric tapes (AC_M). Open circles and closed circles indicate the data for males and females, respectively.*

in their 20s. The VFA-to-TFA ratio was lower in subjects in their 20s and 30s, and this ratio was consistently lower in females than in males regardless of age. These findings suggest that an increase in visceral fat deposition occurs in the 40s and that the preference of fat deposition for the visceral compartment is more predominant in males than in females.

Relationship between Fat Deposition and AC

Both VFA and SFA correlated with AC_{CT} in both male and female subjects (Fig. 3): $AC_{CT} = 0.142 \times VFA + 67.060$, $r=0.828$, $p<0.0001$, $AC_{CT} = 0.126 \times SFA + 65.616$, $r=0.795$, $p<0.0001$. The regression line for the relationship between VFA and AC_{CT} did not differ between males and females ($Y = 0.128X + 68.517$ *vs.* $Y = 0.182X + 64.536$). As expected, TFA was strongly correlated with AC_{CT} ($r=0.815$ in males and 0.919 in females), whereas there was no significant correlation between AC_{CT} and VFA-to-SFA ratio in either gender. However, the regression line for the SFA-AC_{CT} relationship was significantly shifted upwards in females compared with that in males ($Y = 0.139X + 67.076$ *vs.* $Y = 0.123X + 61.594$, $p<0.05$ by analysis of co-variance), indicating a larger contribution of SFA to AC_{CT} in females. Since directly measured AC_M is currently used for diagnosis of visceral obesity in the criteria of metabolic syndrome, we examined the relationship between AC_{CT} and AC_M in 80 randomly selected subjects. There was a tight correlation between AC_{CT} and AC_M, as shown in Fig. 4. The regression equation for the AC_M-AC_{CT} relationship ($Y = 1.023X + 0.830$) suggests that the difference between AC_{CT} and AC_M is only a few percent on average.

Cutoff Points of VFA and AC_M for Prediction of Metabolic Syndrome and ASCD

Since VFA is a more direct measure of visceral obesity than AC_M, we used ROC analysis to detect VFA cutoff points to predict the presence of two or more components of metabolic syndrome (Fig. 5A). Although the areas under the curves (AUC) were not large, indicating that the results had limited accuracy, the VFA values of 92 cm^2 in males and 63 cm^2 in females predicted the presence of metabolic syndrome with sensitivities of 0.612 and 0.673 and specificities of 0.507 and 0.608, respectively. The exclusion of subjects on antidiabetic medications ($n=81$) from the ROC analysis did not markedly change the VFA cutoffs for predicting two or more metabolic syndrome components (97 cm^2 in males and 55 cm^2 in females).

As another method to assess the clustering of components of metabolic syndrome with increase in VFA, we also calculated the odds ratio for the presence of two or more metabolic syndrome components (except for visceral obesity) at each level of VFA. As shown in Fig. 6, the VFA cutoff giving the highest odds ratio of metabolic syndrome was 94 cm^2 in males and 74 cm^2 in females, which was consistent with the results of ROC analysis (Fig. 5). Figure 5B shows the results of ROC analysis for prediction of ASCD by VFA. At a VFA cutoff of 97.5 cm^2 in males, the sensitivity and the specificity were 0.612 and 0.504, respectively, and at a VFA cutoff of 74.6 cm^2 in females, the sensitivity and specificity were 0.602 and 0.526, respectively. These VFA cutoff values correspond to AC_M values of 84 cm in males and 80 cm in females.

We also performed ROC analysis using SFA and TFA to predict two or more components of metabolic syndrome. However, the AUC was smaller in the ROC using SFA or TFA than in the ROC using VFA (data not shown), supporting the notion that VFA is better than SFA or TFA as an index for diagnosis of metabolic syndrome.

Discussion

In the present study, we first characterized VFA, a direct index of visceral obesity, and its relationship with an indirect but easily used index of visceral obesity, AC_M. Using VFA as a basic tool, we reassessed the cutoff level of AC_M for diagnosis of visceral obesity relevant to metabolic syndrome in Japanese. The results of ROC analysis indicate cutoff levels of 92 cm^2 in males and 63 cm^2 in females, which correspond to AC_M values of 83 cm in males and 78 cm in females. This male AC_M cutoff is almost the same as the current cutoff level (85 cm), but the female AC_M cutoff was considerably smaller than the current Japanese criterion (90 cm). The validity of the new AC_M cutoff level for females needs to be further examined using larger numbers of subjects.

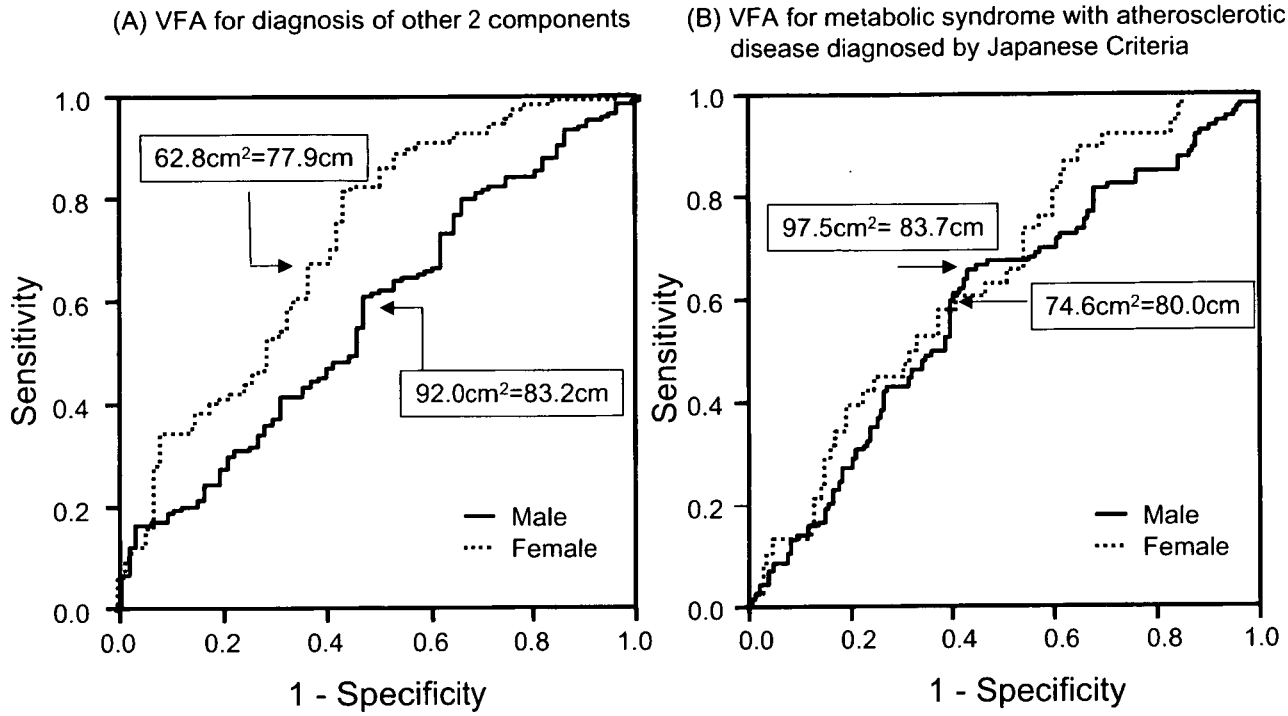

Fig. 5. *Receiver operating characteristic (ROC) analysis of VFA to predict the presence of two or more components of metabolic syndrome and ASCD. Solid lines and broken lines depict the ROC curves for males and females, respectively.*

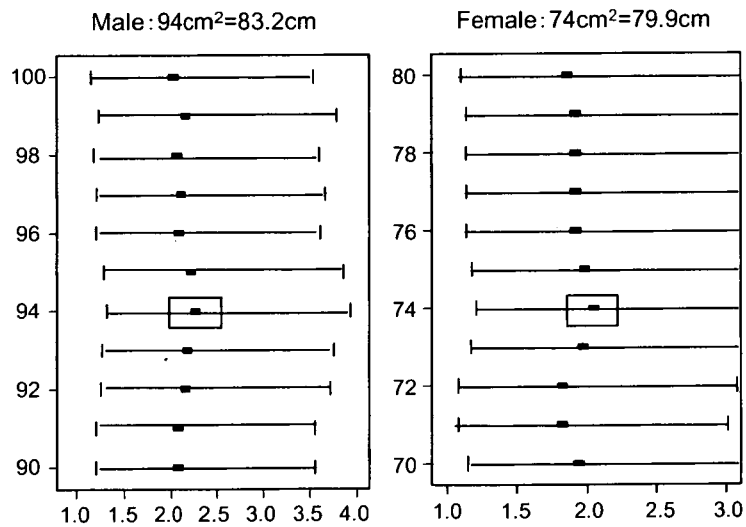

Fig. 6. *Odds ratio for the presence of two or more components of metabolic syndrome at each level of VFA. An odds ratio was calculated for every cm² of VFA and is presented along with the confidential interval. The highest odds ratio was given by a VFA of 94 cm² in males and by a VFA of 74 cm² in females.*

Definition of Visceral Obesity as a Component of Metabolic Syndrome in Japanese

In both the latest criteria by IDF (*8*) and the Japanese criteria (*9*), visceral obesity is a requisite factor in metabolic syndrome. The cutoff levels of AC_M in the Japanese criteria (*i.e.*, 85 cm in males and 90 cm in females) were defined as the values that correspond to VFA of 100 cm² in abdominal CT in each gender. The rationale for this level of VFA was the association of VFA larger than 100 cm² with more than one obesity-related disease (*i.e.*, hyperglycemia, dyslipidemia and hypertension) in the pooled data from both males and