transcription indirectly via another transcriptional factor. Analysis of the α-SMA promoter is now underway to prove this hypothesis.

Although STZ rats were thought to be useful to study the mechanisms of functional changes in the early phase of diabetic nephropathy, they were inappropriate to examine the relationship between functional and structural changes, because glomerular structural changes occurred in STZ rats vary in incidence and severity.[12,27] In this study, we could examine their variety of glomerular structure clearly showed that there was no association of functional changes with the severity of glomerular structural changes in this model. Furthermore, the validity of this morphometric analysis was supported by our result that the expression of Col4 and α-SMA was significantly correlated with the severity of mesangial matrix expansion. Thus, this morphometric analysis for mesangial PASM-positive area used in this study would be a useful method for studying about mesangial matrix expansion in STZ rats.

Here, we have also found that glomerular injuries occurred in STZ rats can mimic those occurred in the early phase of human diabetic nephropathy, in terms of the association between functional and structural changes. There are several characteristics, but yet unsolved manifestations in the early phase of human diabetic nephropathy. For example, although nearly all patients have glomerular hyperfiltration in this phase, only part of these patients develops diabetic nephropathy.[11] Next, even if glomerular structural changes occur, the rates of progression often differ from one another and vary greatly among patients.[4] It is reported that albuminuria does not reflect the severity of glomerular structural changes of diabetic nephropathy.[5] It is generally accepted that albuminuria predicts the late development of diabetic nephropathy. However, in our study, albuminuria was not correlated with mesangial matrix expansion, which is a predictor for declining of GFR in the late stage. These problems are also found in early human diabetic nephropathy.[6,7] In this study, we investigated the hyperfiltration stage, which is separated from the late progression stage. We speculate that this argument might come from the difference of the stage in the development of diabetic nephropathy. Therefore, further examination about STZ rats using this morphometric analysis will uncover the mechanism of these manifestations occurred in human early diabetic nephropathy. For this reason, we next checked the correlation of the molecules examined in this study with albuminuria or Cre clearance. We found statistically significant correlation between α-SMA and both Cre clearance ($r=0.457$, $P<0.05$) and albuminuria ($r=0.597$, $P<0.05$). It is very intriguing that glomerular expression of α-SMA was significantly correlated with variables of glomerular hemodynamics. The mesangial cells may have several important beneficial functions in the glomeruli, one of which is the modulation of glomerular hemodynamics via their contractile properties.[28] Our results would indicate the association of glomerular hemodynamics with contractile components in diabetic nephropathy. We also found that glomerular expression of α-SMA was correlated with albuminuria. However, this finding could be mistakenly deduced from some statistical outliers, although not statistically confirmed in these small sample numbers. Furthermore, evidence is accumulating on the possible pathogenesis of albuminuria dissociated from that of mesangial expansion,[29] supported by the observation that long-term treatment of db/db mice with blocking antibody against TGF-β suppressed glomerular mesangial matrix expansion in the absence of significant modulation of albuminuria.[30] Further examination of STZ rats will elucidate the molecular mechanisms on the relationship between functional and glomerular structural changes.

It is very intriguing that urinary excretion of Smad1 was significantly increased only in STZ rats with diabetic glomerular structural changes. Because diabetic glomerular structural changes are characterized by the accumulation of ECM, the measurement of matrix molecules, such as Col4 in the urine has recently been considered as a possible marker of diabetic glomerular structural changes. However, changes in these markers do not generally increase until the relatively late phase of the disease. At this stage, renal biopsy is the only way to detect the earlier stages of the disease.[31] Although monitoring urinary TGF-β seems attractive,[32] the highly ubiquitous nature of this cytokine and the existence of multiple circulating forms make it difficult to interpret the results. Another attractive report showed that urinary CTGF was upregulated in STZ rat prior to the development of albuminuria.[33] However, it remained to be elucidated whether CTGF could reflect glomerular structural changes especially in the early phase of diabetic nephropathy. In our study, we have confirmed that urinary Smad1 was closely correlated with the severity of mesangial matrix expansion in diabetic rats. Thus, it is suggested that urinary Smad1 could be a better noninvasive diagnostic marker for mesangial matrix expansion in the early phase of diabetic nephropathy.

In summary, this is the first demonstration that Smad1, a direct regulatory factor of Col4 in mesangial cells, also plays a key role for glomerular structural changes in experimental diabetic nephropathy, and that the expression of this key molecule in glomeruli is closely related to the diabetic structural changes. Urinary Smad1 could be a better diagnostic marker for mesangial matrix expansion in the early phase of diabetic nephropathy than albuminuria.

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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)

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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

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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.

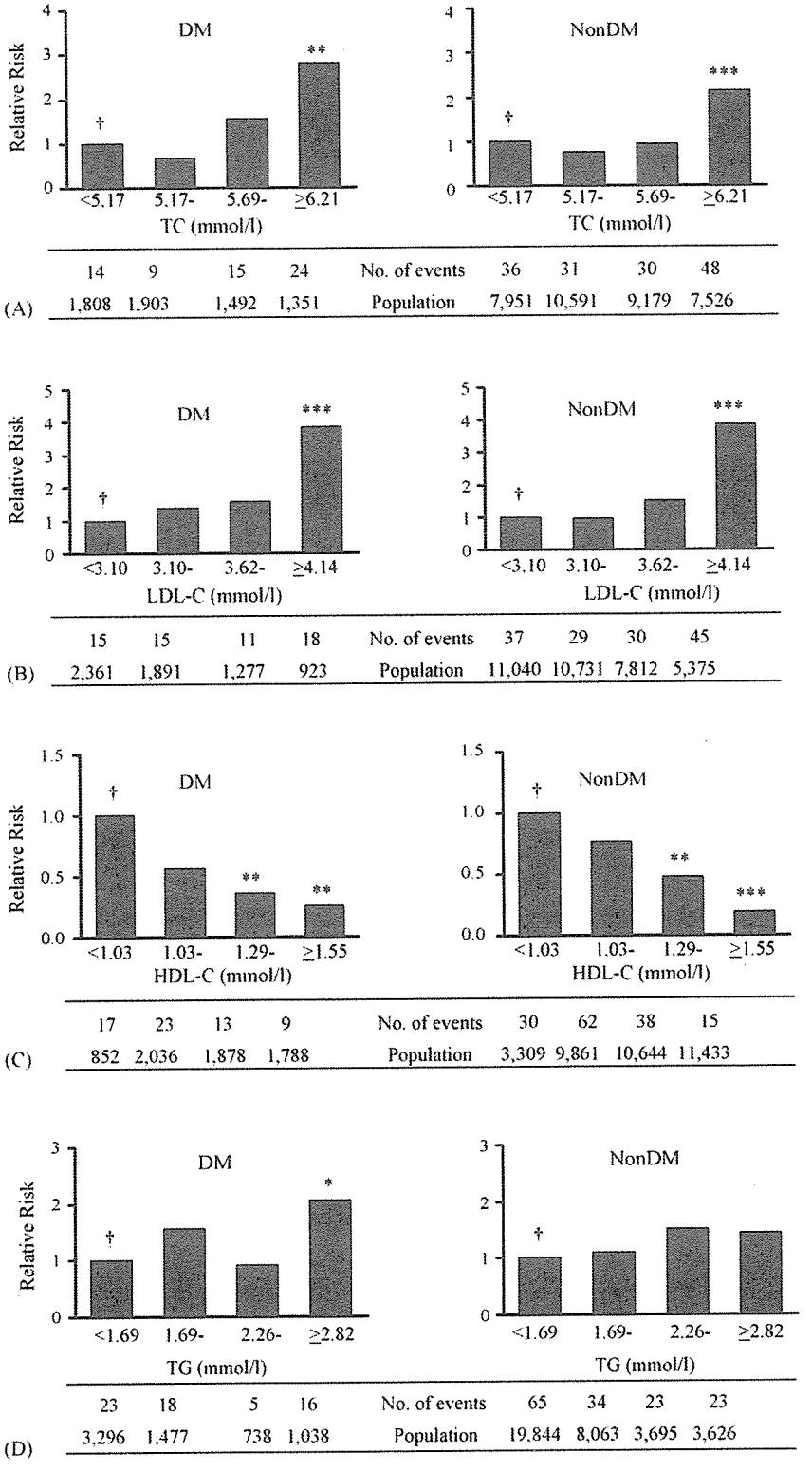

Fig. 1. Relative risk of coronary events based on lipid total cholesterol (TC) (A), low density lipoprotein-cholesterol (LDL-C) (B), high density lipoprotein-cholesterol (HDL-C) (C) and triglycerides (TG) (D) levels during treatment for patients with and without diabetes. Coronary events: myocardial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

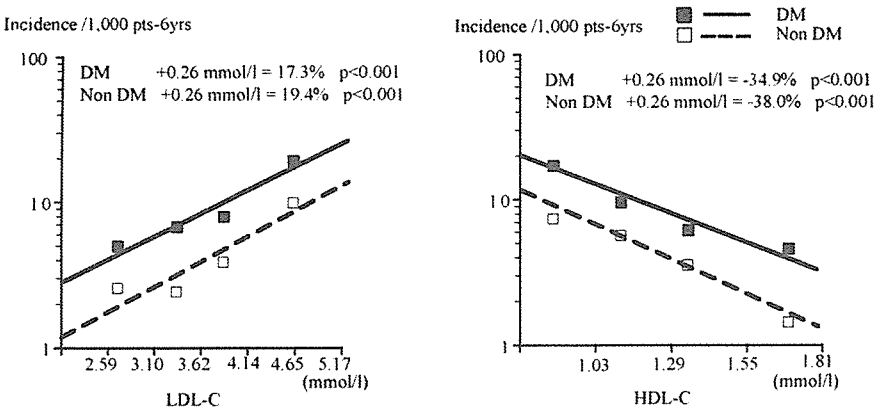

Fig. 2. The incidence of coronary events and lipid levels during treatment. Coronary events: myocardial infarction and sudden cardiac death. DM, type 2 diabetes. Adjusted with sex, age, hypertension, fasting blood glucose, and smoking habit.

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

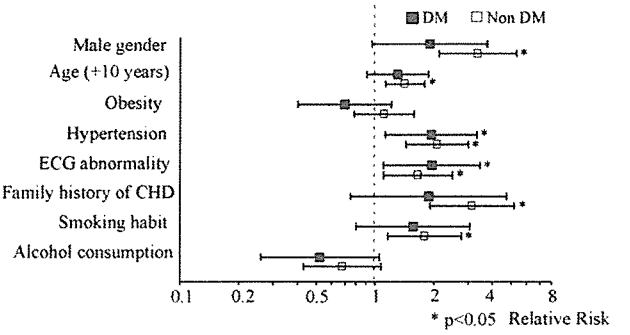

Fig. 3. Relative risk of coronary events by baseline characteristics. Coronary events: myocardial infarction and sudden cardiac death. Obesity, body mass index $\geq 25\ kg/m^2$; DM, type 2 diabetes. Adjusted with sex, age, hypertension, electrocardiogram abnormality, family history of CHD, smoking habit,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

Prevalence of Metabolic Syndrome in the General Japanese Population in 2000

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To determine the prevalence of metabolic syndrome in the Japanese general population, we analyzed data from a nationwide survey conducted in 2000. According to the Japanese new diagnostic criteria for metabolic syndrome in 2005, we analyzed 3,264 people aged from 20 to 79 (men, 1,917; women, 1,347) from the total participants. The incidence of metabolic syndrome was 7.8%. Men had a higher incidence (12.1%) than women (1.7%). Most of the women satisfying the criteria were 50 years old or over, while the incidence in men started to rise from their 30s. When we applied the criteria of Adult Treatment Panel III, the incidence was about 3-fold higher. In this population visceral obesity was associated with metabolic abnormalities, such as higher LDL-cholesterol, triglyceride, glucose, and blood pressure and lower HDL-cholesterol. Thus we determined the incidence of metabolic syndrome and each metabolic abnormality in the Japanese general population in 2000 and found an association of visceral obesity with metabolic abnormalities. Intervention to reduce the incidence of metabolic syndrome in Japan is necessary to reduce the risk of cardiovascular disease.

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Introduction

Metabolic syndrome is a constellation of multiple risk factors, such as dyslipidemia, elevated glucose, and elevated blood pressure. This syndrome has received increased attention due to its association with increased risk for cardiovascular disease and type 2 diabetes[1]. Although the pathogenesis of metabolic syn-

drome has not been fully understood, the predominant underlying risk factor is considered to be visceral obesity due to an atherogenic diet and physical inactivity in the presence of some unknown genetic background[2-4]. In women the incidence of metabolic syndrome increases after menopause; therefore, hormonal imbalance and aging are also associated with the development of metabolic syndrome[5].

Along with the westernization of lifestyle, the incidence of metabolic disorders, such as dyslipidemia, hypertension, and diabetes is increasing in Japan. In spite of the availability of many drugs, such as statins, angiotensin-converting enzyme inhibitors, and aspirin, the incidence of cardiovascular disease is not decreasing in Japan, probably due to these metabolic abnormalities, especially dyslipidemia and diabetes along with obesity according to the national survey by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/toukei/saikin/hw/kenkou/jyunkan/jyunkan00/gaiyo.html). In 2000, we conducted a lipid survey in various districts in Japan[6]. What we found in this survey was that the level of triglyceride increased in middle-aged men along with increased body mass index (BMI) compared with the data in 1990[7]. This increase in BMI also suggests an increase in the incidence of visceral obesity and metabolic syndrome; therefore, knowing the incidence of metabolic syndrome is very important from the standpoint of preventive medicine.

In the last few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients with metabolic syndrome. The committee of International Diabetes Federation (IDF) adopted waist circumference as the surrogate marker for visceral obesity as an essential component of this syndrome (http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf). In Japan the committee established diagnostic criteria under the same principle as that used in the IDF criteria, except that the cutoff point for high glucose is 110 mg/dL instead of 100 mg/dL[8]. The cutoff of waist circumference for visceral obesity was adopted as ≧85 cm in men and ≧90 cm in women. Meanwhile, the National Cholesterol Education Program (NCEP) Adult Treatment Panel Ⅲ (ATP Ⅲ) criteria required no single factor for diagnosis, but instead required the presence of at least 3 out of 5 components for diagnosis[9]; thus, complete agreement on the definition and diagnostic criteria has not been achieved so far.

The purpose of this study is to examine the incidence of metabolic syndrome in the Japanese general population and the relationship with the risk factors included in the diagnostic criteria. We also compared the incidence of metabolic syndrome by using the NCEP-ATP Ⅲ new diagnostic criteria.

Methods

Design and Data Collection

The Research Group on Serum Lipid Level Survey 2000 in Japan organized the members of 36 institutes from various areas around Japan. The project was designed to produce representative data about serum lipid levels in the civilian Japanese population. The subjects were people receiving annual health examinations in the general community, companies, and schools, and not patient-visiting hospitals. Among the 12,839 participants we measured the waist circumference of 3,264 people aged 20 to 79 (men 1,917; women, 1,357) and examined the incidence of metabolic syndrome.

Laboratory Methods

All serum and plasma samples were obtained in the fasting state. All lipid and other analyses were conducted on venous blood samples within one week of collection at BML (Saitama, Japan). Serum cholesterol and triglyceride levels were measured by enzymatic assay. HDL-cholesterol and LDL-cholesterol were measured enzymatically using a kit from Daiichi Kagaku Co. Ltd. (Tokyo, Japan). The results of lipid analyses in the four surveys were indirectly standardized according to the criteria of the CDC Lipid Standardization Program[10]. Thus, the cholesterol levels in these five surveys appear comparable. Plasma glucose was determined enzymatically and HbA1c was determined using a kit from Kyowa Medex Co.Ltd (Tokyo, Japan). Serum insulin was determined by immunoradiometric assay (Abbott Diagnostics Division, Abbot Park, IL). Waist circumference at the umbilical level was measured in the late exhalation phase in a standing position.

Definition of Metabolic Syndrome

According to the new definition released by the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome in April 2005, we defined metabolic syndrome as the presence of 2 or more abnormalities in addition to visceral obesity (waist circumference: 85 cm or more in men, 90 cm or more in women). These three abnormalities are as follows: 1, triglycerides ≧150 mg/dL and/or HDL-cholesterol <40 mg/dL or under treatment for this type of dyslipidemia, 2, systolic blood pressure ≧130 and/or diastolic blood pressure ≧85, or under treatment for hypertension, 3, fasting glucose ≧110 mg/dL or under treatment for diabetes. People treated for dyslipid-

Table 1. Clinical characteristics of the study population

	men (n=1,917)	women (n=1,347)
age	46.3 ± 0.30	45.7 ± 0.46
BMI	23.4 ± 0.07	22.4 ± 0.07*
waist circumference (cm)	84.1 ± 0.20	73.2 ± 0.29*
systolic blood pressure (mmHg)	125 ± 0.40	120 ± 0.49*
diastolic blood pressure (mmHg)	76.3 ± 0.27	72.3 ± 0.31*
T-cho (mg/dL)	201 ± 0.78	200 ± 0.97
TG (mg/dL)	145 ± 2.97	92.1 ± 1.64*
HDLc (mg/dL)	54.8 ± 0.33	64.6 ± 0.39*
LDLc (mg/dL)	118.0 ± 0.99	113.5 ± 1.22**
HbA1c (%)	4.86 ± 0.02	4.82 ± 0.14
fasting glucose (mg/dL)	97.8 ± 0.43	91.1 ± 0.36*
insulin (IU/mL)	6.28 ± 0.11	7.16 ± 0.21*

Data are expressed as the means ± SEM. T-cho; total cholesterol, TG; triglyceride, HDLc; HDL-cholesterol, LDLc; LDL-cholesterol. *$p < 0.001$, **$p < 0.01$

Table 2. Incidence of metabolic syndrome and metabolic abnormalities by Japanese diagnostic criteria

	men (%)	women (%)	all (%)
metabolic syndrome	12.1	1.7	7.8
visceral obesity	48.2	9.7	32.3
hypertriglyceridemia	31.3	11.2	23.0
low HDL-cholesterolemia	12.4	2.2	8.2
dyslipidemia	35.2	12.1	25.6
hypertension	25.4	19.5	22.9
elevated fasting glucose	14.4	7.0	11.3

Dyslipidemia is defined as hypertriglyceridemia and/or low HDL-cholesterolemia

emia were excluded, because we could not obtain data as to whether they were treated for hypercholesterolemia or hypertriglyceridemia. We also analyzed the incidence of metabolic syndrome by ATP Ⅲ criteria published in 2005[9]. We modified the criteria by using the Japanese cutoff of waist circumference. Other differences are fasting glucose ≧100 mg/dL and HDL-cholesterol <50 mg/dL in women. Metabolic syndrome in ATP Ⅲ criteria was defined as the presence of at least 3 abnormalities among visceral obesity, hypertriglyceridemia, low HDL-cholesterolemia, hypertension, and glucose intolerance.

Data Analysis

The results are expressed as the mean value ± standard deviation, and categorical data by the incidence and relation between visceral obesity and various factors were expressed by the odds ratio and 95% confidence interval. Differences in the means were evaluated by analysis of variance (ANOVA) or analysis of covariance (ANCOVA). The relation between visceral obesity and various factors was examined using multiple, logistic regression analysis for multivariate analysis. Analysis was performed using the statistical Package for Social Sciences (SPSS Japan Inc. ver. 11.5, Tokyo, Japan). A p value of 0.05 or less was considered to indicate significant difference.

Results

Table 1 shows the characteristics of the study population. The means of total cholesterol, triglyceride, HDL-cholesterol, and fasting glucose were 200 mg/dL, 123 mg/dL, 59 mg/dL, and 95 mg/dL. These data are almost the same as the means of the total participants (201, 115, 59, 95, respectively)[6]. The means of both genders were also equivalent to the means of the total participants, indicating that this population represents all participants in this Japanese lipid survey in 2000. Although we found no difference in the mean age, total cholesterol, and HbA1c between men and women, the means of BMI, waist circumference, blood pressure, triglyceride, LDL-cholesterol, and fasting glucose were higher in men than in women, while those of HDL-cholesterol and insulin were lower in men than in women.

Using the Japanese diagnostic criteria for metabolic syndrome we determined the incidence of metabolic syndrome (**Table 2**). The incidence of metabolic syndrome in all participants was 7.8%. The incidence in men and women was 12.1, 1.7%, respectively. The incidence was about 7-fold higher in men than in women, reflecting the difference in visceral obesity defined by waist circumference, 48.2% in men and 9.7% in women. The incidence of dyslipidemia, hypertension, and glucose intolerance was also higher in men than in women in this population, indicating a higher prevalence of metabolic abnormalities in men.

It is important for us to intervene from the period of visceral obesity to prevent cardiovascular disease due to these metabolic abnormalities. Therefore, we compared the incidence of visceral obesity, visceral obesity plus one metabolic abnormality, and metabolic syndrome. **Fig. 1** shows the incidence of visceral obesity, visceral obesity plus one metabolic abnormality, and metabolic syndrome. The incidence of visceral obesity plus one metabolic abnormality was about twice the incidence of metabolic syndrome both in men and women.

To compare the incidence of metabolic syndrome

by Japanese and ATP Ⅲ criteria in this population, we determined the incidence of metabolic syndrome using these criteria in each generation from age 20s to 70s in men and women as shown in **Fig. 2**. The incidence of metabolic syndrome using ATP Ⅲ criteria was about 3 times higher than that by the Japanese criteria. Using both criteria the incidence of metabolic syndrome started to rise in men in their 30s and reached a plateau after their 40s. Meanwhile, the incidence of metabolic syndrome in women started to rise after their 50s using both criteria, indicating the increased prevalence of metabolic syndrome after menopause.

We next examined whether visceral obesity contributed to metabolic abnormalities in this study population. **Fig. 3** shows the difference of lipid profiles and fasting glucose levels with or without visceral obe-

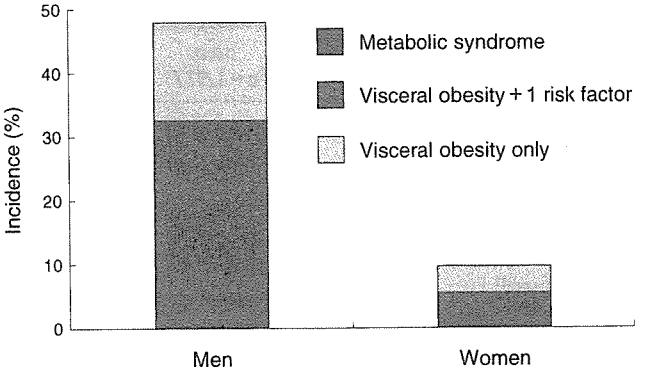

Fig. 1. Incidence of metabolic syndrome and visceral obesity in the lipid survey in 2000.

The percent incidence of metabolic syndrome, visceral obesity plus one risk factor, and visceral obesity in men and women is shown.

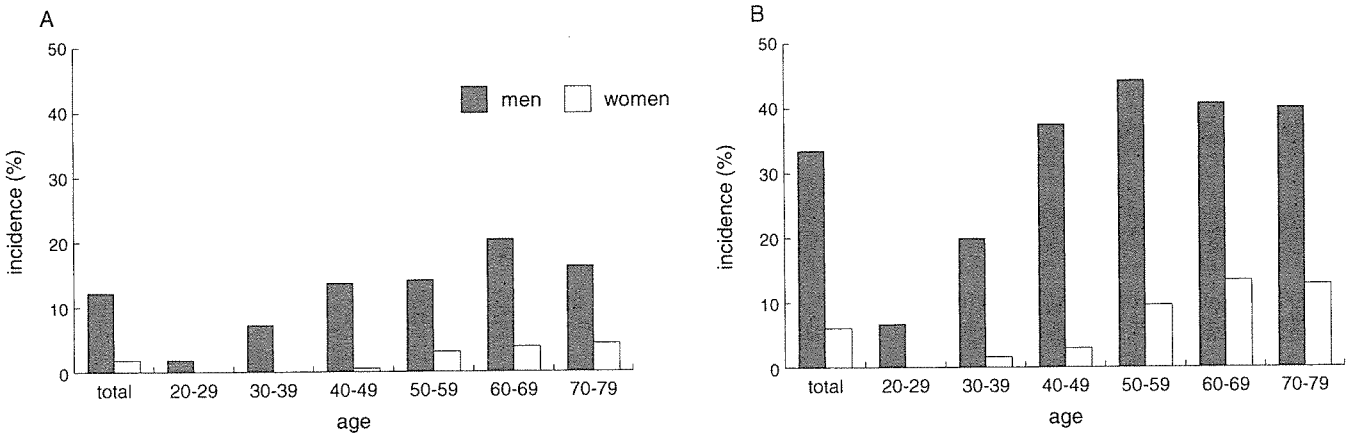

Fig. 2. Incidence of metabolic syndrome in each generation by Japanese and ATP Ⅲ criteria.

Each column shows the incidence of metabolic syndrome in each generation in men (closed column) and women (open column) by Japanese (A) and ATP Ⅲ (B) criteria. The incidence in the total population is shown on the left.

Fig. 3. Comparison of metabolic abnormalities with or without visceral obesity.

Each column shows the mean ± SD of total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, and fasting glucose with or without visceral obesity in men (A) and women (B). $^{*}p < 0.001$

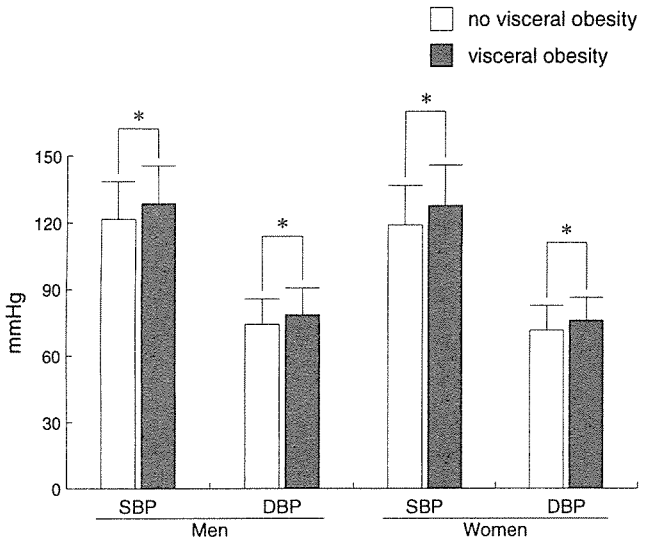

Fig. 4. Comparison of systolic and diastolic pressure with or without visceral obesity.

Each column shows the mean ± SD of systolic and diastolic blood pressure with or without visceral obesity in men and women. $^{*}p < 0.001$

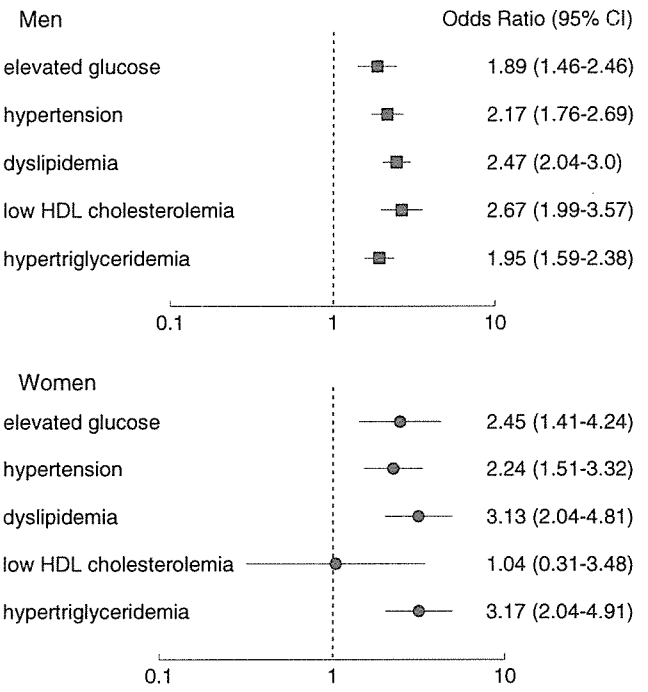

Fig. 5. Effect of visceral obesity on hypertriglyceridemia, low HDL cholesterolemia, dyslipidemia, hypertension, and glucose intolerance in men and women.

Odds ratios and 95% confidence interval are shown for each abnormality in the presence or absence of visceral obesity.

sity in this study population. The levels of total cholesterol, triglyceride, LDL-cholesterol, and fasting glucose were significantly higher, while the level of HDL-cholesterol was significantly lower in the group with visceral obesity than in the group without, indicating the contribution of visceral obesity to these metabolic abnormalities in both men and women. Systolic and diastolic blood pressure was also higher in the visceral obesity group in both genders (**Fig. 4**). We also determined the effect of visceral obesity on the development of each abnormality by calculating the odds ratios and 95% confidence interval (**Fig. 5**). Visceral obesity was significantly associated with the development of each metabolic abnormality in men and women except for low HDL-cholesterolemia in women. When we changed the cutoff of HDL-cholesterol to 50 mg/dL, visceral obesity was significantly associated with low HDL-cholesterolemia in women. The odds ratio was 2.10 and the 95% confidence interval was 1.35-3.27. Among dyslipidemia, hypertension, and glucose intolerance, visceral obesity was most associated with the development of dyslipidemia.

We also determined the age-adjusted difference of lipid profile in the presence or absence of visceral obesity in this population. Even after age adjustment we found a significant difference in total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol in men and in women, except for a difference in LDL-cholesterol in women (**Table 4**).

Discussion

In this study we determined the incidence of metabolic syndrome in the Japanese general population using a lipid survey performed in 2000 using new Japanese criteria to diagnose metabolic syndrome. We found that 3 times more people were diagnosed with metabolic syndrome using the new ATP Ⅲ criteria than the Japanese criteria and that visceral obesity contributed to metabolic abnormalities, such as dyslipidemia, glucose intolerance, and hypertension.

In our study the incidence of metabolic syndrome in Japanese men and women was 12.1 and 1.7%, respectively. The incidence of metabolic syndrome in our survey is lower than that from the latest National Health and Nutrition survey in 2004. In that survey the incidence of metabolic syndrome in Japanese men and women was 23.0 and 8.9%, respectively. In this national survey they used HbA1c (≧5.5) instead of FBS to diagnose glucose intolerance. This might explain the difference between the two surveys. This difference also indicates that the cutoff of FBS needs to be changed in the future. Although the mean age and the criteria used were different, Takeuchi *et al.*

Table 3. Incidence of each metabolic abnormality in the presence or absence of visceral obesity

	visceral obesity		no visceral obesity	
	men	women	men	women
hypertriglyceridemia	41.1%	25.4%	22.2%	9.7%
low HDL-cholesterolemia	17.6%	2.3%	7.4%	2.2%
dyslipidemia	45.7%	26.9%	25.4%	10.5%
hypertension	32.8%	33.1%	18.4%	18.1%
elevated fasting glucose	18.4%	14.6%	10.6%	6.2%

Dyslipidemia is defined as hypertriglyceridemia and/or low HDL-cholesterolemia

Table 4. Age-adjusted difference of lipid profile in the presence or absence of visceral obesity

		men		age-adjusted	women		age-adjusted	all		age-adjusted
		no visceral obesity	visceral obesity	*P*	no visceral obesity	visceral obesity	*P*	no visceral obesity	visceral obesity	*P*
T-cho	mean	195.6	205.9		198.8	214.2		197.3	206.9	
	number	994	923	<0.001	1217	130	0.082	2211	1053	<0.001
	SD	33.4	33.4		35.4	33.1		34.6	33.4	
TG	mean	128.7	162.0		88.9	121.7		106.8	157.0	
	number	994	923	<0.001	1217	130	<0.001	2211	1053	<0.001
	SD	119.3	138.8		60.2	51.5		93.7	131.8	
HDLc	mean	57.7	51.7		65.1	59.8		61.8	52.7	
	number	994	923	<0.001	1217	130	0.003	2211	1053	<0.001
	SD	14.2	13.9		14.5	12.5		14.8	14.0	
LDLc	mean	112.1	122.1		111.4	128.0		111.7	122.9	
	number	374	479	0.001	510	71	0.106	884	550	<0.001
	SD	26.0	30.1		29.0	28.8		27.8	30.0	

The mean, the number of samples, and SD are shown. *P* value was obtained by ANCOVA.

reported that the incidence of metabolic syndrome in men in the Tanno and Sobetsu study was 25.3%[11]. The mean age of their study population was 60.3 years, about 15 years older than that in our study population. Other studies reported a similar incidence of metabolic syndrome in Japanese. Considering that the incidence of metabolic syndrome in our population in their 60s was about 20%, the difference of the criteria used contributed to this difference. Similar to our study Urashima *et al.* reported an incidence of metabolic syndrome in Japanese men and women of 14.1% and 1.7%, respectively in central Tokyo[12]. Thus, the current incidence of metabolic syndrome in Japan would be around 15% in men and a few percent in women. In our study we found that about twice as many people with metabolic syndrome had visceral obesity and one risk factor in both men and women, indicating a potential for the incidence of metabolic syndrome to increase in the future. In our previous analysis we showed that the level of triglyceride in men dramatically increased from 1990 to 2000[6]. Therefore, we need to tackle this problem to prevent the increase in metabolic syndrome and cardiovascular disease in Japan.

In this population the incidence of metabolic syndrome in women was one seventh that in men. The incidence of visceral obesity, dyslipidemia, and glucose intolerance in women was one fifth, one third, and one half that in men, respectively. Furthermore, most of the women who satisfied this criteria were more than 50 years old, which means that few women are diagnosed with metabolic syndrome before the menopause. In Japan we adopted a cutoff of waist circumference of 90 cm for women, which is 5 cm more than that for men. This might explain why the incidence of metabolic syndrome in women was much less than in men. In contrast to the cutoff waist circumference in Japan, other criteria, such as in ATP III,

generally have a larger cutoff in men than in women; however, our cutoff in women is based on the extensive study by Matsuzawa and his group using CT scan[13-15]. Therefore, in terms of detecting visceral obesity, 90 cm would be appropriate for Japanese women. However, we need to establish another method to select high-risk patients without visceral obesity. Our data also strongly indicate that visceral obesity using our cutoff is associated with metabolic abnormalities even after age adjustment, as shown in **Fig. 5** and **Table 4**. Therefore, we believe that visceral obesity is a useful surrogate marker for metabolic abnormalities and intervention to reduce abdominal circumference would lead to the prevention of cardiovascular disease. However, in terms of the cutoff of HDL-cholesterol, 50 mg/dL might be better than 40 mg/dL from the odds ratio in women (**Fig. 5** and Results) as in the cutoff of the ATP III criteria.

In summary we have shown that the incidence of metabolic syndrome in the Japanese general population is 7.8%, 12.1% in men and 1.7% in women. Intervention is required to prevent metabolic syndrome as well as metabolic abnormalities, such as dyslipidemia, hypertension, and glucose intolerance. The current criteria for metabolic syndrome should be assessed for the better diagnosis of women and elderly people.

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ORIGINAL ARTICLE

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Measurements of baseline and follow-up concentrations of cardiac troponin-T and brain natriuretic peptide in patients with heart failure from various etiologies

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Abstract Since chronic heart failure (CHF) is a complex clinical syndrome, a single biomarker may not reflect all of its characteristics. In this study, the clinical significance of combination and serial measurement of biochemical markers of myocyte injury and myocardial load in patients with CHF from various etiologies was examined. Serum concentrations of cardiac troponin-T (cTnT) and plasma concentrations of brain natriuretic peptide (BNP) were measured simultaneously in 190 patients with CHF, including dilated cardiomyopathy (DCM) ($n = 41$), ischemic heart disease ($n = 40$), valvular or congenital disease ($n = 53$), hypertensive heart disease ($n = 16$), and hypertrophic cardiomyopathy (HCM) ($n = 22$). Serum cTnT concentrations ≥0.01 ng/ml were found in 46/190 patients (24%) at baseline (20% in DCM, 42% in ischemic heart disease, 21% in valvular or congenital disease, 43% in hypertensive heart disease, and 9% in HCM). Follow-up samples were obtained in 137 patients after a mean treatment period of 31.8 days. Although BNP decreased significantly in each disease category ($P < 0.0001$: DCM; $P < 0.005$: ischemic heart disease; $P < 0.05$: valvular or congenital disease; $P < 0.005$: hypertensive heart disease; $P < 0.05$: HCM), cTnT remained high in 36/137 patients (26%) (19% in DCM, 39% in ischemic heart disease, 25% in valvular or congenital disease, 38% in hypertensive heart disease, and 19% in HCM). The rate of adverse cardiac events was significantly higher in patients with high cTnT than in patients with low cTnT concentrations ($P < 0.0001$) ($P < 0.05$: DCM; $P < 0.05$: ischemic heart disease; $P < 0.01$: valvular or congenital disease). Multivariate analysis showed that both cTnT and BNP are independent prognostic factors, and patients with elevations of both cTnT and BNP had the poorest prognosis ($P < 0.0001$). In patients with CHF, the evolution and prognostic value of cTnT and BNP are different. The combined measurements of these markers should refine our understanding of the state and evolution of CHF.

Key words Troponin · Brain natriuretic peptide · Heart failure

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Introduction

Chronic congestive heart failure (CHF) is associated with a dismal long-term prognosis and remains a major health concern worldwide,[1,2] though grading its severity remains a challenge. New York Heart Association (NYHA) functional classification and several tests, including chest roentgenography, echocardiography, myocardial scintigraphy, cardiopulmonary exercise, and hemodynamic measurements, while helping to estimate the degree of CHF, are however subject to interobserver variations in interpretation. Combination and serial measurements of reliable biochemical markers would provide a more objective evaluation method for patients with CHF.

Cardiac troponin-T (cTnT) is a highly sensitive and specific marker of myocardial injury in acute coronary syndromes, and a revised definition of acute myocardial infarction has been developed, based on rises in cardiac troponins in the blood.[3,4] On the other hand, many reports suggested that an increase in serum cTnT or cardiac troponin I concentrations seems to be a reliable indicator of ongoing subclinical myocyte injury in patients with CHF without apparent ischemic events.[5–10] In contrast, the plasma concentrations of brain natriuretic peptide (BNP), which is produced and released by cardiac myocytes, correlate with cardiac filling pressures. Therefore, plasma BNP has been proposed as (a) a marker of ventricular dysfunction, (b) a diagnostic tool in presence of cardiac dyspnea, (c) an endpoint in the monitoring of CHF therapy, and (d) a prognostic marker in CHF.[11,12] Since CHF is a complex clini-

cal syndrome, a single biomarker may not reflect all of its characteristics.

Theoretically, cTnT is a marker of myocyte injury while BNP reflects cardiac load.[8] This retrospective study examined the contribution of combined measurements of cTnT and BNP measured simultaneously in the evaluation of patients with CHF from various etiologies, in the absence of acute coronary syndrome.

Patient population and methods

The study population consisted of 190 consecutive patients admitted to the Kyoto University Hospital between July 2001 and December 2003 for management or evaluation of CHF. No patient had sustained a myocardial infarction or suffered from unstable angina pectoris within 3 months prior to hospitalization, and no electrocardiographic changes or increase in creatine kinase enzyme were present upon admission. Patients with end-stage cancer, pulmonary hypertension, pulmonary embolism, myocarditis, degenerative disease of the muscles, or patients undergoing hemodialysis were not included in this analysis. Clinical diagnosis was made based on disease history, echocardiographic findings, myocardial scintigraphy, and/or cardiac catheterization. The diagnosis of dilated cardiomyopathy and hypertrophic cardiomyopathy was based on the definition of the WHO/ISFC task force.[13] The demographic and baseline clinical characteristics of the study population are presented in Table 1.

Serum cTnT (Roche Diagnostics, Tokyo, Japan) and plasma BNP (Shionogi, Osaka, Japan) were measured with commercially available immunoassay kits. The lower detection limit of third generation cTnT is 0.01 ng/ml, and values ≥0.01 ng/ml were considered abnormal.[14] All study procedures were in compliance with the ethical institutional guidelines of Kyoto University.

Long-term clinical events

Major adverse cardiac events were defined as sudden death without apparent acute coronary syndrome, death from CHF, or rehospitalization of the patient for management of cardiac decompensation. The criteria for a diagnosis of cardiac decompensation used in this study were (1) dyspnea or orthopnea requiring hospitalization, intravenous furosemide, and infusion of nitrates or inotropic agents, and (2) roentgenographically apparent pulmonary edema and presence of moist rales on auscultation. Information pertinent to a patient's mode of death occurring outside the hospital was obtained from the family. Operations for patients with valvular and congenital heart diseases were not considered as cardiac events and follow-up periods of these patients were calculated as days from entry to operations.

Statistical analysis

Continuous variables were compared by factorial analysis of variance, and categorical variables were compared by

Table 1. Characteristics of overall study population and of subgroups of patients with various underlying cardiovascular disorders

	All patients (n = 190)	DCM (n = 41)	Ischemic heart disease (n = 40)	Valvular or congenital disease (n = 53)	Hypertensive heart disease (n = 16)	HCM (n = 22)	Others (n = 18)
Age, years (mean ± SE)	65.0 ± 0.9	63.1 ± 2.0	66.4 ± 2.2	63.7 ± 1.7	68.1 ± 4.0	65.9 ± 2.2	66.3 ± 3.2
Men/women	116/74	30/11	35/5	29/24	8/8	11/11	3/15
NYHA functional class							
I	41	6	10	8	2	12	3
II	70	13	12	26	4	6	9
III	48	14	11	11	6	3	3
IV	31	8	7	8	4	1	3
LVEF, % (mean ± SE)	51.6 ± 1.3	34.9 ± 1.8*	38.7 ± 1.7*	62.6 ± 1.8	58.8 ± 3.1	67.9 ± 2.4	59.1 ± 4.1
LVEDd, mm (mean ± SE)	54.9 ± 0.7	61.4 ± 1.0*	59.1 ± 1.2**	53.3 ± 1.5	48.5 ± 1.6	46.9 ± 1.2	51.5 ± 2.6
Baseline drug therapy							
Furosemide	92/190 (48)	24/41 (58)	20/40 (50)	27/53 (51)	9/16 (56)	6/22 (27)	6/18 (33)
Beta-adrenergic blocker	30/190 (16)	7/41 (17)	9/40 (23)	6/53 (11)	1/16 (6)	5/22 (23)	2/18 (11)
ACEI or ARB	78/190 (41)	18/41 (44)	27/40 (67)	13/53 (25)	8/16 (50)	9/22 (40)	3/18 (17)
Follow-up drug therapy							
Furosemide	126/190 (66)	32/41 (78)	28/40 (70)	34/53 (64)	11/16 (69)	10/22 (45)	11/18 (61)
Beta-adrenergic blocker	82/190 (43)	25/41 (61)	21/40 (52)	11/53 (22)	4/16 (25)	16/22 (72)	5/18 (28)
ACEI or ARB	114/190 (60)	32/41 (78)	31/40 (78)	20/53 (38)	12/16 (75)	10/22 (45)	9/18 (50)

Unless specified otherwise, values indicate numbers (%) of patients

DCM, dilated cardiomyopathy; valvular or congenital disease, aortic regurgitation (n = 14), aortic stenosis (n = 9), mitral regurgitation (n = 13), mitral stenosis (n = 2), atrial septal defect (n = 5), ventricular septal defect (n = 2), tetralogy of Fallot (n = 1), corrected transposition of the great arteries (n = 1), postvalve operation (n = 5), postatrial septal defect operation (n = 1); HCM, hypertrophic cardiomyopathy; others, tachyarrhythmia-induced heart failure (n = 7), cardiac amyloidosis (n = 4), cardiac sarcoidosis (n = 6) restrictive cardiomyopathy (n = 1)

NYHA, New York Heart Association; LVEF, echocardiographic left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

* $P < 0.0001$ vs valvular or congenital disease, hypertensive heart disease, and HCM

** $P < 0.05$ vs valvular or congenital disease, hypertensive heart disease, and HCM

Table 2. Baseline cardiac troponin-T (cTnT) and brain natriuretic peptide (BNP) concentrations in various disease subgroups

Underlying heart disease	DCM ($n = 41$)	Ischemic heart disease ($n = 40$)	Valvular or congenital disease ($n = 53$)	Hypertensive heart disease ($n = 16$)	HCM ($n = 22$)	Others ($n = 18$)
Baseline						
Creatine kinase concentration, IU/l (mean ± SE)	89.3 ± 5.6	87.1 ± 6.4	85.6 ± 5.7	86.3 ± 10.9	104.9 ± 10.2	71.2 ± 12.2
BNP concentration, pg/ml (mean ± SE)	593.0 ± 127.5*	606.1 ± 123.6*	341.1 ± 66.8	343.5 ± 70.1	354.5 ± 69.1	371.2 ± 64.2
TnT ≥ 0.01 ng/ml						
n (%) of patients	8/41 (20)	17/40 (42)	11/53 (21)	7/16 (43)	2/22 (9)	1/18 (5)
Mean concentration, ng/ml (mean ± SE)	0.039 ± 0.008	0.069 ± 0.017	0.039 ± 0.010	0.051 ± 0.005	0.035 ± 0.005	0.090

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy
* $P < 0.05$ vs valvular or congenital disease, hypertensive heart disease, and HCM

chi-square analysis. Changes occurring between time points during follow-up were analyzed by two-tailed Student's paired t-test. Cardiac event-free actuarial curves were constructed by the Kaplan–Meier method, and compared by log-rank test. The prognostic value of the variables was tested in a Cox proportional hazard regression analysis. Data are expressed as mean ± standard error. A P value of less than 0.05 was considered significant.

Results

Baseline cTnT and BNP concentrations

Baseline cTnT was ≥0.01 ng/ml in 46/190 patients (24%). The results among the various disease subgroups are shown in Table 2. Elevated cTnT concentrations were found in 5%–43% of patients with various cardiovascular diseases without acute coronary syndrome. Mean creatine kinase (CK) and cTnT concentrations for all the subgroups were identical. Brain natriuretic peptide concentrations were significantly elevated in patients with DCM ($P < 0.05$) and ischemic disease ($P < 0.05$) compared with those in other groups.

The mean baseline BNP concentrations in patients in NYHA functional classes I, II, III, and IV were 140.2 ± 20.0 ($n = 41$), 248.7 ± 36.7 ($n = 70$), 670.3 ± 80.0 ($n = 48$), and 1009.6 ± 179.8 ($n = 31$) pg/ml, respectively. Corresponding cTnT concentrations measured simultaneously were ≥0.01 ng/ml in 2/41 (5%), 11/70 (16%), 16/48 (33%), and 17/31 (55%). In patients in NYHA functional classes I, II, III, and IV whose cTnT was ≥0.01 ng/ml, the mean concentrations were, respectively, 0.085 ± 0.065 ($n = 2$), 0.070 ± 0.024 ($n = 11$), 0.040 ± 0.007 ($n = 16$), and 0.050 ± 0.006 ($n = 17$) ng/ml (no significant differences).

Follow-up measurements of cTnT and BNP

As this study is retrospective, we could not obtain 53 follow-up blood samples. Follow-up measurements of cTnT and BNP during treatment of CHF were obtained simultaneously at a mean of 31.8 ± 1.9 days in 137 patients. In the entire group, follow-up BNP (259.4 ± 30.1 pg/ml) was significantly lower than at baseline (549.1 ± 57.9, $P < 0.0001$). In subgroups according to underlying diseases, BNP decreased significantly between baseline and follow-up in patients with dilated cardiomyopathy ($P < 0.0001$), ischemic disease ($P < 0.005$), valvular or congenital disease ($P < 0.05$), hypertensive heart disease ($P < 0.005$), hypertrophic cardiomyopathy ($P < 0.05$), and miscellaneous cardiac disorders ($P < 0.05$) (Table 3). In contrast, serum cTnT concentrations ≥0.01 ng/ml were found in 19% of DCM, 39% of ischemic heart disease, 25% of valvular or congenital disease, 38% of hypertensive heart disease, and 19% of HCM patients, at follow-up. Increased cTnT concentrations were observed in 40/137 (29%) of patients at baseline and in 36/137 (26%) of patients at follow-up. Mean cTnT concentrations were identical in each disease category at baseline and at follow-up (Table 3).

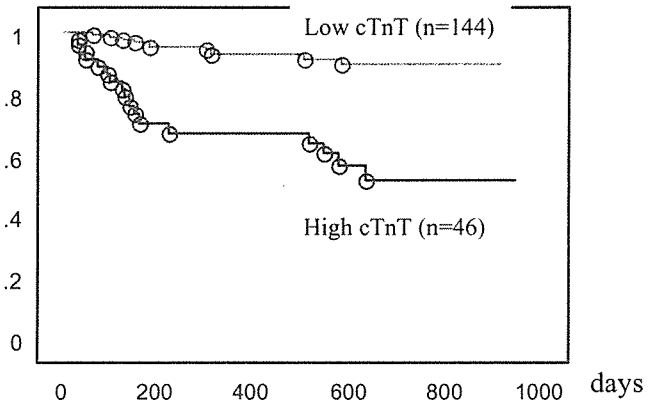

Fig. 1. Adverse cardiac event-free rate in patients with cardiac troponin-T (*cTnT*) concentrations ≥0.01 ng/ml (*high*) versus patients with low cTnT concentrations. The event-free rate was significantly higher in patients with low than in patients with high cTnT concentrations ($P < 0.0001$)

Baseline cTnT concentrations and long-term outcomes

Among the 46 patients with baseline cTnT concentrations ≥0.01 ng/ml, 17 (37%) sustained an adverse cardiac event. In contrast, among 144 patients with low baseline cTnT concentrations, 9 (6%) sustained an adverse cardiac event ($P < 0.0001$, Fig. 1). The adverse cardiac event rates were