TABLE 2. Distribution of ALDH2 Gene Genotypes in Patients With Pancreatic Cancer and Control Subjects

Male	Pancreatic Cancer (n = 70) n (%)	Control Subjects (n = 1050) n (%)
Genotype		
ALDH2*1/2*1 (active ALDH)	26 (37.1)*	544 (51.8)
ALDH2*1/2*2 (inactive ALDH)	36 (51.4)	413 (39.3)
ALDH2*2/2*2 (inactive ALDH)	8 (11.4)	93 (8.9)
Female	**Pancreatic Cancer (n = 44) n (%)**	**Control Subjects (n = 1020) n (%)**
Genotype		
ALDH2*1/2*1 (active ALDH)	22 (50.0)	513 (50.3)
ALDH2*1/2*2 (inactive ALDH)	19 (43.2)	414 (40.6)
ALDH2*2/2*2 (inactive ALDH)	3 (6.8)	93 (9.1)

*The frequency was significantly lower compared with that in control subjects (χ^2 = 5.65, df = 1, P = 0.018).
The difference between the wild-type genotype and the mutations (the sum of the inactive form) was tested by 2 × 2 χ^2 test.

DISCUSSION

The present study showed that a smoking habit with or without a drinking habit is a risk factor for pancreatic cancer in male subjects as previously reported.[2] In contrast, alcohol drinking has no relation to pancreatic cancer. When the effect of drinking with or without smoking was investigated, the frequency of drinking habits did not differ between pancreatic cancer patients and control subjects, regardless of ALDH2 genotype (P = 0.53).

On the other hand, in spite of no relation between drinking and pancreatic cancer, the frequency of subjects with inactive ALDH2 was significantly higher in male pancreatic cancer patients than in control subjects. ALDH2 is responsible for metabolizing the acetaldehyde produced from ethanol into acetate. The inactive form of ALDH2 is considered to produce high levels of acetaldehyde to be accumulated in the blood, which has been known to be an animal carcinogen. We did not measure the blood concentration of acetaldehyde in the present study. In the previous report by Harada et al,[16] the acetaldehyde concentrations in the blood were significantly higher in subjects with inactive ALDH2 than those with active ALDH2 after 0.5 g/kg ethanol was administered orally (35.3 ± 12.8 μmol/L in 19 subjects with inactive ALDH2 vs. 2.1 ± 1.7 μmol/L in 25 subjects with active ALDH2), while the ethanol concentrations were comparable (10 mmol/L).

When the effect of smoking with or without drinking was investigated, the frequency of a smoking habit was significantly higher in pancreatic cancer patients than in control subjects. The frequency of male subjects who had both smoking and drinking habits was similar between subjects with ALDH2*1/2*1 and ALDH2*1/2*2 in both pancreatic cancer patients and controls (Table 3). In subjects with ALDH2*1/2*2, the frequency of smokers in pancreatic cancer (80%) was 2 times that of control (40%) (Table 3), and more subjects with pancreatic cancer had both smoking and drinking habits than control subjects. The odds ratio in the subjects with ALDH2*1/2*1 was 2.14 and 6.1 in the subjects with ALDH2*1/2*2. No subjects with ALDH2*1/2*1 had a smoking habit alone; however, 10 of the ALDH2*1/2*2 subjects had a smoking habit alone (Table 3). In contrast, only 2 patients (ALDH2*1/2*2) had a drinking habit alone. Therefore, a smoking habit would mask the contribution of acetaldehyde. Insofar as subjects with ALDH2*2/2*2 can hardly drink alcohol because of an inability to eliminate acetaldehyde, which causes an adverse reaction, known as the flushing response, after ethanol ingestion. Indeed, none of the 8 pancreatic cancer patients with ALDH2*2/2*2 had a drinking habit. Four of the ALDH2*2/2*2 subjects had a smoking habit (Table 3), although the difference between the pancreatic cancer patients and the controls was not significant (P = 0.44) (Table 3). It is suggested that the subjects with inactive ALDH2 might prefer to or be forced to smoke rather than drink during social intercourse. We did not determine how much ethanol or how much tobacco were consumed; thus, we could not further stratify these groups.

TABLE 3. Smoking and/or Drinking Habits and ALDH2 Gene Polymorphism in Male Pancreatic Cancer Patients and Control Subjects

Genotype	Both Smoking and Drinking Habits	Smoking Habit Alone	Drinking Habit Alone	Neither Habit	Total n (%)
Pancreatic cancer patients					
ALDH2*1/2*1	16 (61.5)*	0 (0)	8 (30.8)	2 (7.7)	26 (100)
ALDH2*1/2*2	19 (52.8)†	10 (27.8)‡	2 (5.6)	5 (13.9)	36 (100.1)
ALDH2*2/2*2	0 (0)	4 (50)	0 (0)	4 (50.0)	8 (100)
Control subjects					
ALDH2*1/2*1	184 (33.8)	18 (3.3)	291 (53.5)	54 (9.4)	544 (100)
ALDH2*1/2*2	109 (26.4)	58 (14.0)	125 (30.3)	121 (29.3)	413 (100)
ALDH2*2/2*2	1 (1.1)	31 (33.3)	3 (3.2)	58 (77.4)	93 (100)

*df = 1, P = 0.006, odds ratio = 3.13.
†df = 1, P = 0.002, odds ratio = 3.12.
‡df = 1, P = 0.048, odds ratio = 2.35.
The difference was tested by the Fisher direct test.

TABLE 4. Smoking and/or Drinking Habits, and ALDH2 Gene Polymorphism in Female Subjects

Genotype	Both Smoking and Drinking Habits	Smoking Habit Alone	Drinking Habit Alone	No Habit	Total n (%)
Pancreatic cancer patients					
ALDH2*1/2*1	1 (4.5)	3 (13.6)	2 (9.1)	16 (72.7)	22 (100)
ALDH2*1/2*2	0 (0)	1 (5.2)	1 (5.2)	17 (89.5)	19 (100)
ALDH2*2/2*2	0 (0)	1 (33.3)	0 (0)	2 (66.7)	3 (100)
Control subjects					
ALDH2*1/2*1	19 (3.7)	11 (2.1)	168 (32.7)	315 (61.4)	513 (100)
ALDH2*1/2*2	5 (1.2)	32 (7.7)	56 (13.5)	321 (77.5)	414 (100)
ALDH2*2/2*2	1 (1.1)	3 (3.2)	3 (3.2)	86 (92.5)	93 (100)

There were no significant differences.

Because few Japanese women have smoking and/or drinking habits, a relationship between smoking and pancreatic cancer was not significant. However, tendencies of higher frequency of subjects who had a smoking habit (13.6% for pancreatic cancer vs. 7% for controls) and of lower frequency of subjects who had a drinking habit (9% for pancreatic cancer vs. 24.8% for controls) in pancreatic cancer patients were observed in female subjects as well as in male subjects. The sex difference in habits might be one reason why the incidence of pancreatic cancer is higher in Japanese men than in women.

In conclusion, a smoking habit increased the risk of pancreatic cancer regardless of the presence or absence of a drinking habit, and smoking enhanced the risk of pancreatic cancer in male subjects having inactive ALDH2.

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The Contribution of Cardiorespiratory Fitness and Visceral Fat to Risk Factors in Japanese Patients With Impaired Glucose Tolerance and Type 2 Diabetes Mellitus

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It is still unclear as to how cardiorespiratory fitness and visceral fat accumulation contribute to coronary heart disease (CHD) risk factors in patients with diabetes mellitus. The purpose of the present study was to investigate whether cardiorespiratory fitness contributes to such risk factors independently of visceral fat accumulation. Two hundred Japanese patients (137 men and 63 women, aged 22 to 81 years) with impaired glucose tolerance (IGT) and type 2 diabetes mellitus (type 2 DM) without any intervention and pharmacological therapy participated in a cross-sectional study. The levels of fasting insulin, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and resting blood pressure were assessed. Maximal oxygen uptake ($\dot{V}O_{2max}$), an index of cardiorespiratory fitness, was predicted by a graded exercise test using a cycle ergometer. Visceral fat area (VFA) was measured by computed tomography scan. The criteria for abnormalities of the risk factors were determined according to the standard values for Japanese. All subjects were divided equally into the following 3 groups according to their fitness level: low-fit ($\dot{V}O_{2max}$ < 32 mL/kg/min in men, $\dot{V}O_{2max}$ < 26 mL/kg/min in women), mid-fit (32 ≤ $\dot{V}O_{2max}$ < 36 in men, 26 ≤ $\dot{V}O_{2max}$ < 30 in women), and high-fit ($\dot{V}O_{2max}$ ≥ 36 in men, $\dot{V}O_{2max}$ ≥ 30 in women). The association between fitness level and the prevalence of abnormal values for these parameters was analyzed by a multiple logistic regression model adjusted for age and VFA. The odds ratio (OR) and 95% confidence interval (CI) for the prevalence of hyperinsulinemia were significantly lower in the mid-fit (OR = 0.35, 95% CI, 0.16 to 0.78) and in the high-fit groups (OR = 0.40, 95% CI, 0.16 to 0.98) compared with the low-fit group. In addition, ORs for the prevalence of low HDL-C in the mid-fit and high-fit groups were significantly lower (OR = 0.35, 95% CI, 0.14 to 0.86; and OR = 0.19; 95% CI, 0.08 to 0.60, respectively) than in the low-fit group. These results suggested that cardiorespiratory fitness might be one of the predictors of metabolic abnormalities, especially in patients with hyperinsulinemia and low HDL-C, independent of visceral fat accumulation in Japanese patients with IGT and type 2 DM.

THE ASSOCIATION of visceral fat accumulation and metabolic impairment is widely known.[1-3] Nagaretani et al[3] reported that Japanese patients with impaired glucose tolerance (IGT) had a greater visceral fat area (VFA) and more unfavorable profile of risk factors than controls. They simultaneously pointed out that VFA was an independent factor of clustering of metabolic abnormalities such as hyperinsulinemia, dyslipidemia, and hypertension regardless of the presence/absence of glucose intolerance. The clustering of these risk factors has previously been described as "syndrome X"[4] and "the deadly quartet."[5] In 1989, the World Health Organization proposed a definition for the clustering of these risk factors and called it the "metabolic syndrome."[6] They are considered to be the result of an aggravation of insulin resistance, which is also strongly related to visceral fat accumulation.[7-10]

On the other hand, several studies have demonstrated the contribution of cardiorespiratory fitness and/or physical activity to such risk factors. A recent cross-sectional study[11] reported that fitness level evaluated by maximal exercise time during a treadmill test was inversely associated with a clustering of risk factors (elevated systolic blood pressure, hypertriglyceridemia, hyperglycemia, and elevated central adiposity) in a large sample (N = 19,437). Another cross-sectional study in middle-aged men also indicated the contribution of cardiorespiratory fitness and physical activity to the lipid metabolism profile and fasting blood glucose level after adjusting for age and body mass index (BMI).[12] In addition, prospective studies by Wei et al[13-15] reported that low cardiorespiratory fitness was an independent predictor to increase the risk of cardiovascular diseases and all-cause mortality after adjusting for other risk factors.

Both visceral fat accumulation and cardiorespiratory fitness are therefore considered to be significant predictors for metabolic abnormalities. However, it has yet to be confirmed which is an independent predictor of metabolic abnormality. Until now, few studies investigated the contribution of visceral fat accumulation and cardiorespiratory fitness to coronary heart disease (CHD) risk factors.[16-18] Kumagai et al[16] reported that cardiorespiratory fitness, defined as oxygen uptake at the onset of blood lactate accumulation, was independently related to triglyceride (TG), high-density lipoprotein cholesterol (HDL-C)/total cholesterol (TC), and insulin area, while the waist-to-hip ratio (WHR), an indirect index of abdominal fat accumulation, was only related to TG independently in obese individuals. In obese postmenopausal women with normal metabolic profiles, cardiorespiratory fitness was the strongest predictor of HDL-C, while visceral fat accumulation was the strongest predictor of insulin sensitivity and TG.[17] The available evidence concerning this matter remains insufficient. Especially regarding patients with IGT and type 2 DM who tend to demonstrate clusters of metabolic abnormalities,[3] no report

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has so far investigated which factors may be independent predictors for each CHD risk factor. According to a prospective study by Batty et al,[19] physical activity evaluated by walking pace and level of leisure-time activity may play a beneficial role in reducing the CHD risk in men with IGT and type 2 DM. If so, a favorable level of cardiovascular fitness might effectively reduce the CHD risk even in the patients who have large amounts of visceral fat. Therefore, the present study attempted to investigate the independent contribution of visceral fat accumulation and cardiorespiratory fitness to hyperinsulinemia, dyslipidemia, and hypertension in patients with IGT and type 2 DM.

MATERIALS AND METHODS

Subjects

Two hundred Japanese patients (137 men and 63 women, aged 22 to 81 years) who had been diagnosed as having IGT and type 2 DM by 75-g oral glucose tolerance test (OGTT) participated in this study. The pathological state was classified by the diagnostic criteria of the Committee of Japan Diabetes Society.[20] Although 2 to 24 months passed from the time that the patients were determined to have an elevated blood glucose level at a group medical checkup, none had received any pharmacological therapy or intervention. The present study was conducted with the approval of the Ethics Committee of the Institute of Health Science, Kyushu University, and informed consent for all procedures was obtained from all patients.

Measurement of Metabolic Parameters

The values of metabolic parameters were obtained from the diagnostic test for diabetes mellitus. The subjects visited the hospital early in the morning after an overnight fasting of at least 12 hours. After taking fasting blood samples, a 75-g OGTT was performed. Blood samples were obtained at 30, 60, 120, and 180 minutes. Fasting insulin and fasting blood glucose concentrations were measured by a radioimmunoassay and an enzymatic method, respectively. Levels of fasting TG, TC, and HDL-C were assessed by the enzymatic method. The area under the curve for insulin (AUC_{IRI}) and blood glucose (AUC_{BG}) during the 75-g OGTT were also calculated by the trapezoidal rule using absolute values. Resting systolic (SBP) and diastolic blood pressure (DBP) were determined 3 times following a 30-minute rest period using a mercury sphygmomanometer, and the lowest values were used as the resting blood pressure. The subjects newly diagnosed to have IGT or type 2 DM were told to undergo an anthropometric evaluation and a fitness test as soon as possible. All of the subjects took the second assessment within 2 to 3 weeks from the diagnostic test.

Assessment of Lifestyle

The patients answered a questionnaire to assess their alcohol use, smoking habit, and weekly exercise habit. Concerning alcohol use and smoking habit, we regarded cases with no history of alcohol use and smoking as an "absence" of each habit. Regarding exercise, the frequency within 1 week, subjective intensity, duration, and period of the exercise were assessed.

Anthropometric Evaluation

BMI was calculated as weight (kilograms) divided by height (meters) squared. Body fat percentage (%Fat) was estimated based on the sum of the triceps and subscapular skinfolds measured with a skinfold caliper using Brozek's formula.[21] Waist circumference was measured at the level of the umbilicus. Both visceral (VFA) and subcutaneous fat area (SFA) were automatically calculated by a computer system connected to a computed tomography scan (Vigor Lau Dator, Toshiba, Japan) as described by Tokunaga et al.[22]

Evaluation of Cardiorespiratory Fitness

Graded exercise tests using a cycle ergometer (Monark, Stockholm, Sweden) were performed to evaluate cardiorespiratory fitness by the same skilled examiner. Heart rate, electrocardiograms, and blood pressure were monitored and recorded during the test. Exercise intensity was increased 3 or 4 times every 4 minutes until the heart rate reached 70% of maximum or above. Maximal oxygen uptake ($\dot{V}o_{2max}$) was predicted by the nomogram of Åstrand and Rhyming,[23] a modality that is generally used to predict the $\dot{V}o_{2max}$, which is regarded as an index of cardiovascular fitness.

Criteria for Abnormality of Risk Factors

We defined the abnormalities in these risk factors using the following standard values for the Japanese population: high TC: TC $\geq$ 220 mg/dL,[24] high TG: TG $\geq$ 150 mg/dL,[24] low HDL-C: HDL-C $<$ 40 mg/dL,[24] hypertension: SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg.[25] Regarding hyperinsulinemia, there is no standard diagnostic value for Japanese at present. We therefore adopted fasting insulin $\geq$ 7 μU/mL, a 75th percentile value of fasting insulin of Japanese male workers reported by Tamakoshi et al,[26] as the basic criteria for hyperinsulinemia in this study.

Classification of Cardiovascular Fitness

The subjects were divided equally into 3 groups according to their fitness level for each sex. The lower class, the middle class, and the higher class were regarded as (1) low-fit group: $\dot{V}o_{2max} < 32$ mL/kg/min in men and $\dot{V}o_{2max} < 26$ mL/kg/min in women; (2) mid-fit group: $32 \leq \dot{V}o_{2max} < 36$ in men and $26 \leq \dot{V}o_{2max} < 30$ in women; and (3) high-fit group: $\dot{V}o_{2max} \geq 36$ in men and $\dot{V}o_{2max} \geq 30$ in women, respectively.

Statistical Analysis

An analysis of variance (ANOVA) and the Tukey-Kramer post-hoc test were used to compare the physical and metabolic characteristics of the IGT and type 2 DM groups in each sex. TG, fasting insulin, and AUC_{IRI} had skewed distributions and were analyzed after log-transformation (Table 1). Comparisons of the characteristics among the 3 different fitness groups were performed using a chi-square analysis and ANOVA (Table 2). The odds ratio (OR) and 95% confidence interval (CI) for the prevalence of any abnormality in the risk factors were calculated using a multivariate logistic regression model based on the presence/absence of an abnormality for each risk factor as a dependent variable (Table 3). Stat View version 5.0 software (SAS Institute, Chicago, IL) was used for the analysis. Statistical significance was accepted at a value of $P < .05$.

RESULTS

Characteristics of Subjects

Table 1 shows the physical and metabolic characteristics of the patients with IGT and type 2 DM in both sexes. Significant differences among the 4 groups were observed in age, %Fat, $\dot{V}o_{2max}$, SFA, fasting blood glucose, AUC_{BG}, AUC_{IRI}, TG, and HDL-C by ANOVA. Significant pathology-related differences were recognized in age, fasting blood glucose, AUC_{BG}, and AUC_{IRI} in men, and were recognized in age, fasting blood glucose, AUC_{BG}, and AUC_{IRI} in women by the Tukey-Kramer post-hoc test. In addition, significant sex differences were recognized in %Fat, $\dot{V}o_{2max}$, and SFA in the patients with IGT,

Table 1. Characteristics of the Subjects

Valuables	Male		Female		Sex Difference	
	IGT (n = 31)	Type 2 DM (n = 106)	IGT (n = 17)	Type 2 DM (n = 46)	IGT	DM
Age (yr)	49.2 ± 9.9	54.2 ± 10.0†	47.4 ± 11.9	56.1 ± 9.1†		
BMI (kg/m^2)	24.9 ± 4.8	24.6 ± 2.7	26.6 ± 5.6	25.6 ± 4.1		
% Fat	20.8 ± 8.9	20.0 ± 5.4	34.2 ± 12.4	35.3 ± 9.5	*	*
$\dot{V}o_{2max}$ (mL/kg/min)	34.9 ± 6.2	33.9 ± 4.6	27.6 ± 7.3	28.8 ± 5.3	*	*
VFA (cm^2)	152.7 ± 56.5	170.8 ± 57.4	141.2 ± 43.9	153.7 ± 54.2		
SFA (cm^2)	150.8 ± 85.7	136.5 ± 67.4	240.5 ± 124.9	227.0 ± 84.2	*	*
Fasting blood glucose (mg/dL)	108.8 ± 9.9	152.4 ± 33.0†	106.8 ± 12.5	144.8 ± 29.1†		
Fasting insulin (μU/mL)	5.8 ± 3.1	6.9 ± 5.4	9.6 ± 6.0	6.8 ± 4.2		
AUC_{BG} (mg/dL)	460.2 ± 48.9	728.6 ± 155.8†	461.3 ± 40.6	708.6 ± 145.0†		
AUC_{IRI} (μU/mL)	143.9 ± 177.7	87.3 ± 76.8†	197.3 ± 130.8	110.1 ± 89.4†		*
TC (mg/dL)	208.3 ± 37.0	219.2 ± 36.4	221.5 ± 38.7	230.7 ± 37.7		
TG (mg/dL)	136.0 ± 75.6	166.8 ± 108.6	100.5 ± 41.2	134.4 ± 89.2		
HDL-C (mg/dL)	50.7 ± 13.9	48.9 ± 12.3	56.9 ± 15.2	56.8 ± 14.5		*
SBP (mm Hg)	132.4 ± 17.3	131.4 ± 15.8	124.5 ± 14.5	136.8 ± 22.8		
DBP (mm Hg)	84.7 ± 10.3	82.8 ± 10.9	77.1 ± 9.2	84.4 ± 12.5		

NOTE. Values are means ± SD.
*Significant sex difference ($P < .05$) in IGT and type 2 DM patients by the post-hoc test.
†Significant difference ($P < .05$) between IGT and type 2 DM patients in each sex by the post-hoc test.

and were recognized in %Fat, $\dot{V}o_{2max}$, SFA, AUC_{IRI}, and HDL- C in the patients with type 2 DM by the post-hoc test.

The subjects were divided into 3 groups according their fitness level as presented in Table 2. No significant differences were observed in the percentage of male/female, IGT/type 2 DM, presence/absence of alcohol use, and smoking habit by the chi-square analysis. A significant difference was observed in percentage of presence/absence of exercise habit at least once per week among the 3 groups. In addition, significant differences were recognized in age, BMI, $\dot{V}o_{2max}$, waist girth, VFA, SFA, fasting insulin, TG, HDL-C, SBP, and DBP among the 3 groups. No significant difference was observed in TC. Further, significant differences were observed in the prevalence of hyperinsulinemia, low HDL-C, and hypertension among the 3

Table 2. Characteristics of Subjects Classified Into Three Cardiovascular Fitness Levels

Valuables	Fitness Category			P
	Low (n = 65)	Moderate (n = 70)	High (n = 65)	
Male/female (%)†	72.3/27.7	65.7/34.3	67.7/32.3	
IGT/type 2 DM (%)†	24.6/75.4	22.9/77.1	24.6/75.4	
Alcohol use (no/yes, %)†	26.6/73.4	34.8/65.2	38.1/61.9	
Smoking habit (no/yes, %)†	44.4/55.6	59.4/40.6	53.2/46.8	
Regular exercise (no/yes, %)†	57.7/42.3	39.0/61.0	33.3/66.7	*
Age (yr)	48.7 ± 13.8	55.5 ± 8.9	51.9 ± 12.0	*
BMI (kg/m^2)	28.7 ± 5.4	24.4 ± 2.5	23.1 ± 2.7	*
$\dot{V}o_{2max}$ (mL/kg/min)	27.3 ± 4.0	31.7 ± 3.1	38.2 ± 4.9	*
Waist girth (cm)	95.8 ± 11.7	86.7 ± 5.8	83.3 ± 7.5	*
VFA (cm^2)	197.8 ± 60.1	160.1 ± 52.7	125.6 ± 42.9	*
SFA (cm^2)	229.5 ± 127.4	151.2 ± 63.6	137.2 ± 60.6	*
Fasting insulin (μU/mL)	10.7 ± 8.4	6.1 ± 3.1	5.2 ± 2.8	*
TC (mg/dl)	222.2 ± 38.9	222.6 ± 35.9	216.2 ± 36.0	
TG (mg/dL)	172.7 ± 119.1	151.2 ± 90.8	123.8 ± 65.6	*
HDL-C (mg/dL)	47.1 ± 14.0	54.0 ± 14.8	53.7 ± 10.7	*
SBP (mm Hg)	134.5 ± 16.0	134.4 ± 19.6	126.5 ± 16.7	*
DBP (mm Hg)	85.6 ± 10.7	84.1 ± 11.1	78.5 ± 10.8	*
Prevalence of hyperinsulinemia (no/yes, %)†	43.1/56.9	77.1/22.9	80.0/20.0	*
Prevalence of high TC (no/yes, %)†	52.3/47.7	41.4/58.6	53.8/46.2	
Prevalence of high TG (no/yes, %)†	55.4/44.6	62.9/37.1	73.8/26.2	
Prevalence of low HDL-C (no/yes, %)†	67.2/32.8	85.7/14.3	92.3/7.7	*
Prevalence of hypertension (no/yes, %)†	48.4/51.6	59.4/40.6	73.4/26.6	*

NOTE. Values are means ± SD.
*Significant difference ($P < .05$) among the 3 groups.
†The chi-square analysis was used.

Table 3. Odds Ratios of Prevalence of Abnormal Values for the Metabolic Parameters Classified by Fitness Level

Variable	Low-Fit	Mid-Fit OR	Mid-Fit 95% CI	High-Fit OR	High-Fit 95% CI
Hyperinsulinemia					
Model 1†		0.26	0.12-0.54*	0.20	0.09-0.44*
	Reference				
Model 2‡		0.35	0.16-0.78*	0.40	0.16-0.98*
High TC					
Model 1		1.42	0.71-2.84	0.89	0.44-1.79
	Reference				
Model 2		1.30	0.63-2.70	0.76	0.34-1.70
High TG					
Model 1		0.83	0.41-1.68	0.47	0.22-0.99*
	Reference				
Model 2		1.34	0.62-2.90	1.10	0.46-2.62
Low HDL-C					
Model 1		0.32	0.14-0.77*	0.17	0.06-0.48*
	Reference				
Model 2		0.35	0.14-0.86*	0.19	0.08-0.60*
Hypertension					
Model 1		0.56	0.28-1.14	0.31	0.15-0.66*
	Reference				
Model 2		0.79	0.37-1.69	0.56	0.24-1.34

NOTE. Values were derived from logistic regression model.
*$P < .05$
†Model 1 was adjusted for age.
‡Model 2 was adjusted for age and VFA.

groups. However, no significant differences were recognized in the prevalence of high TC and high TG among these groups.

Analysis for the Prevalence of Metabolic Abnormalities in Different Fitness Groups

In order to investigate the association between fitness level and the prevalence of any abnormality in the risk factors, either including or excluding the effect of VFA, multivariate logistic regression analysis using the following 2 models were performed; model 1 was adjusted for age, and model 2 was adjusted for age and VFA (Table 3).

The ORs for the prevalence of hyperinsulinemia calculated by model 1 were significantly lower both in the mid-fit group (OR = 0.26, 95% CI, 0.12 to 0.54) and in the high-fit group (OR = 0.20, 95% CI, 0.09 to 0.44) than in the low-fit group. After performing calculations using model 2, the ORs were also significantly lower in the mid-fit group (OR = 0.35, 95% CI, 0.16 to 0.78) and in the high-fit group (OR = 0.40, 95% CI, 0.16 to 0.98) than in the low-fit group. Regarding the prevalence of low HDL-C level, the ORs obtained from model 1 were significantly lower in the mid-fit group (OR = 0.32, 95% CI, 0.14 to 0.77) and in the high-fit group (OR = 0.17, 95% CI, 0.06 to 0.48) than in the low-fit group. The ORs obtained from model 2 were still significantly lower in the mid-fit group (OR = 0.35, 95% CI, 0.14 to 0.86) and in the high-fit group (OR = 0.19, 95% CI, 0.08 to 0.60) compared with that in the low-fit group. Regarding the prevalence of high TG and hypertension, the ORs obtained by model 1 were significantly lower (OR = 0.47, 95% CI, 0.22 to 0.99; OR = 0.31, 95% CI, 0.15 to 0.66, respectively) in the high-fit group compared with the low-fit group, whereas these significances disappeared after analyzing by model 2 (OR = 1.10, 95% CI, 0.46 to 2.62; OR = 0.56, 95% CI, 0.24 to 1.34, respectively). In contrast, ORs for the prevalence of high TC obtained by both models showed no significance in any groups.

A significant difference was observed in the rate of the patients with regular exercise among the 3 groups (Table 2); we therefore calculated the ORs for the prevalence of metabolic abnormality both in the exercise- and non-exercise groups using the same models. However, no significant difference was recognized in the ORs in the exercise group compared with that in the non-exercise group.

DISCUSSION

It has remained unclear whether cardiorespiratory fitness contributes to the risk factors independent of visceral fat, because most such studies tend to discuss these 2 predictors separately. Even in recent prospective studies investigating the effect of cardiorespiratory fitness to the risk factors and mortality,[13-15] neither VFA nor waist circumference was determined. Therefore, the first original point in the present study was that the cardiorespiratory fitness and VFA were simultaneously evaluated, and the contribution of cardiovascular fitness independent of VFA was investigated in each risk factor. The second original point in this study was that the investigation described above was performed in IGT and type 2 DM patients with a higher level of VFA, without any pharmacological therapy and any intervention. The mean VFA of the patients in this study was 161.9 ± 55.4 cm^2, which is 60% higher than the criteria for abdominal obesity (VFA ≥ 100 cm^2) used by the Japan Society for the Study of Obesity.[27] According to this criteria, 86.5% of the patients were diagnosed to have abdominal obesity. It is therefore of interest to clarify whether or not cardiorespiratory fitness is independent of VFA for the prevalence of metabolic abnormalities in such patients.

A middle and high level of fitness was found to be significantly associated with a low prevalence of hyperinsulinemia and low HDL-C without adjusting for VFA. A low prevalence of high TG and hypertension was also significantly associated with a high level of fitness. In addition, a remarkably low prevalence of hyperinsulinemia was still associated with the middle and high levels of fitness after adjusting for VFA. Especially in the prevalence of low HDL-C, the OR was linearly decreased as the fitness level increased. These results suggest that having more than a moderate level of fitness might be associated with a lower risk of both hyperinsulinemia and low HDL-C independent of VFA even in patients with a relatively higher VFA. However, it was speculated that the prevalence of hypertension might depend on VFA.

It should be pointed out that the subjects in this study had different pathological states such as IGT and type 2 DM. We confirmed the pathology-related difference in age and some metabolic variables between IGT and type 2 DM groups in each sex. However, as indicated in Table 2, the percentage of IGT/type 2 DM was not significantly different among the 3 groups classified by fitness level; we then interpreted that an adjustment for pathological state in the logistic regression model was not necessary.

Several reports support our results. Helmrich et al[28] confirmed in a prospective study that physical activity had a protective effect on the occurrence of type 2 DM adjusted for obesity, hypertension, and a parental history of diabetes. In addition, Lynch et al[29] indicated that moderately intense physical activities (5.5 metabolic units or greater) and cardiorespiratory fitness levels of greater than 31.0 mL/kg/min had a protective effect against type 2 DM in middle-aged men. These prospective studies similarly concluded that the effect of cardiorespiratory fitness was particularly strong in men who were at high risk for developing the disease.

Regarding the prevalence of hyperinsulinemia, some reports agree with our results. According to a prospective community study,[30] physical activity and cardiovascular fitness level were inversely associated with fasting insulin concentrations adjusted for waist circumference and the other confounders in nondiabetic men. In addition, an interventional study conducted by Poehlman et al[31] demonstrated that endurance training significantly enhanced glucose uptake without any change in VFA in non-obese women. Similar results in Japanese patients with type 2 DM were obtained in a study of aerobic and resistant programs, which found an improvement in insulin sensitivity without any significant change in BMI.[32] Considering these previous reports and our results, a strong association between fasting insulin level and cardiorespiratory fitness might thus exist independent of VFA.

However, the lipid profile results are more complicated. In cross-sectional studies, Hunter et al[33,34] showed that lipid profile was mainly associated with VFA, and slightly with physical activity. However, they did not determine cardiorespiratory fitness. Dvorak et al[35] indicated a significant association between lipid profile (TC, TG, TC to HDL-C ratio, and low-density lipoprotein cholesterol) and cardiorespiratory fitness rather than physical activity determined by a doubly labeled water method. Because this result was not adjusted for waist circumference, it might have included the effect of visceral fat or other factors. In interventional studies for obese subjects, Tremblay et al[36] reported that although the subjects remained obese after the intervention, cardiovascular exercise training caused favorable changes in their lipid profiles. Our results thus seem to be partially supported by the study because a significant contribution of fitness independent of VFA was only seen in the prevalence of low HDL-C among the lipid metabolism-related parameters. As the present study was cross-sectional study, a larger sample size and prospective and interventional studies are needed to confirm the effects of cardiovascular fitness on lipid metabolism independent of VFA.

We should mention some of the limitations of the present study. As cardiorespiratory fitness was indirectly determined, some errors in $\dot{V}o_{2max}$ could not be avoided. In addition, because the distribution of $\dot{V}o_{2max}$ was relatively narrow in the patients, the range of classification in this study became narrow and slightly shifted to a lower fitness level when compared to Japanese standard values.

In summary, it was suggested that a favorable cardiorespiratory fitness profile might be one of the predictors for a low prevalence of metabolic abnormalities (especially in hyperinsulinemia and low HDL-C) independent of VFA in Japanese patients with IGT and type 2 DM.

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METABOLIC SYNDROME AND RELATED DISORDERS
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Association between Relative Hypogonadism and Metabolic Syndrome in Newly Diagnosed Adult Male Patients with Impaired Glucose Tolerance or Type 2 Diabetes Mellitus

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ABSTRACT

Sex steroid hormones are known to be important regulators of the lipid and glucose metabolism. Lower levels of testosterone (T) or sex hormone-binding globulin (SHBG) have been reported in men with type 2 diabetes. On the other hand, the relationship between relative hypogonadism and metabolic syndrome has not yet to be thoroughly studied. Ninety-eight Japanese adult (age 20–64) male patients with impaired glucose tolerance (IGT) or type 2 diabetes mellitus were divided into either an metabolic syndrome group (n = 42) or a non–metabolic syndrome (n = 56) group according to the definition of metabolic syndrome from WHO, or into three tertiles according to their sex hormone index level. The metabolic syndrome group had a significantly lower T/estradiol (E_2) and SHBG level ($p < 0.01$). The age and subcutaneous fat surface area (SFA) were significantly different within the tertiles in SHBG and T/E_2. Logistic regression analyses were performed to investigate the association between the sex steroid hormone index level and the incidence of metabolic syndrome. Regarding the highest tertiles as a criterion, lower SHBG, T/E_2 or free T/E_2 had a higher odds ratio of prevalence of metabolic syndrome even after adjusting for age and SFA. Relative hypogonadism was strongly associated with the prevalence of metabolic syndrome in Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes.

INTRODUCTION

VISCERAL FAT ACCUMULATION,[1,2] a low level of cardiorespiratory fitness,[3,4] and hypogonadism[5,6] have all been recognized as risk factors for males with coronary heart disease (CHD) and/or type 2 diabetes mellitus. We recently reported cardiorespiratory fitness to be associated with such factors as hyperinsulinemia and a low level of high-density lipoprotein–cholesterol (HDL-c),[7] or the clustering of these risk factors[8] in a group of newly diagnosed Japanese patients with impaired glucose tolerance (IGT) or type 2 diabetes independent of visceral fat accumulation. In the current study, we furthermore investigated the contribution of sex steroid hormones together with visceral fat and cardiorespiratory fitness in the same

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cohort but using only patients ranging in age from 20 to 64 years old.

These risk factors of metabolic impairment—such as "syndrome X"[9] and "the deadly quartet"[10]—have been described in numerous studies. In 1998, the World Health Organization (WHO) defined metabolic syndrome (MS)[11] as a concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia, and hypertension, in order to promote the research and clinical application of this important syndrome. This syndrome also used to be called insulin resistance syndrome because insulin resistance was believed to be the most important pathogenesis and this syndrome is also associated with the subsequent development of type 2 diabetes mellitus as well as cardiovascular disease (CVD),[12,13] which has been reported to be the primary cause of mortality and morbidity in patients with type 2 diabetes.[14] We used the MS definition established by WHO in this study.

In addition to hypertension, hyperlipidemia, and smoking,[15,16] male sex is also an independent risk factor for CVD.[17] Sex steroid hormones were important regulators of the lipid and glucose metabolism and lower levels of testosterone (T) or sex hormone-binding globulin (SHBG), the major serum carrier protein for T, have been reported in men with type 2 diabetes.[18–21] In addition, a population-based prospective study of subjects above the age of 55 with an 8% prevalence of diabetes found an independent inverse association between the levels of T and aortic atherosclerosis in men.[22] Hyperinsulinemia, which is induced by insulin resistance and is a risk factor for CVD,[23] is associated with low concentrations of free and total T in men.[24,25] For any given level of generalized or regional adiposity, men with type 2 diabetes have a significantly higher degree of insulin resistance than non-diabetics.[26] Low plasma levels of free testosterone (FT) are also observed in obesity, particularly in abdominal obesity, a condition that is itself independently accompanied by insulin resistance and heightened risk for type 2 diabetes.[27,28] Compared to men with normal concentrations of T, men with low concentrations of T have a significantly higher body mass index (BMI), waist-to-hip ratio (W/H), as well as systolic blood pressure (SBP), fasting and postprandial plasma glucose concentrations, and fasting serum insulin and total cholesterol (TC) concentrations.[24] Furthermore, the administration of T to hypogonadal rats[29] or humans[30] has resulted in reductions of both abdominal obesity and insulin resistance.

Although the mechanisms underlying the association between hypogonadism and type 2 diabetes are still not entirely understood, it has been postulated that low plasma levels of both SHBG and T contribute to the development of obesity, which, in turn, predisposes such individuals to develop insulin resistance[25,31–37] and, through this effect, to the development of complex metabolic abnormalities that lead to type 2 diabetes in men.[38] On the other hand, the relationship between relative hypogonadism and MS, the cluster of abdominal obesity, glucose and lipid abnormalities, and hypertension, has yet to be thoroughly studied. To our knowledge, only Laaksonen et al.[39] recently reported lower T and SHBG levels in subjects with MS from a population-based study. The comparison of non-diabetic MS versus non-MS subjects in that study is thought to be an appropriate method to study the relationship between relative hypogonadism and MS. However, non-diabetics seldom meet the diagnostic criteria of MS. In addition, the relationship between relative hypogonadism and MS in subjects with abnormal glucose tolerance remains to be unclear. In view of these findings, in the current study, we cross-sectionally investigated 98 Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not previously received either any pharmaceutical treatment or behavior modifying intervention, in order to assess the contribution of relative hypogonadism on the prevalence of MS.

MATERIALS AND METHODS

Ninety-eight Japanese men, aged 20–64, who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not previously received either any pharmaceutical treatment or behavior modifying intervention, were enrolled in this study, which was ap-

proved by the Ethics Committee at Kyushu University (Fukuoka, Japan). All of the patients were diagnosed as having IGT (n = 27) or type 2 diabetes mellitus (n = 71) by a 75-g oral glucose tolerance test (OGTT) in Chikushi Hospital, Fukuoka University (Fukuoka, Japan). None of them were taking any medications at the entry point to the study.

After giving their written informed consent to participate, all subjects were examined for OGTT, sex steroid hormones, lipid metabolic indices, abdominal visceral (VFA) and subcutaneous fat surface areas (SFA) which were automatically calculated by a computer system connected to a computerized tomography (CT) scan (VIGOR LAU DATOR, Toshiba, Japan) as described by Tokunaga et al.,[40] and also underwent anthropometric measurements as well as a cardiorespiratory fitness test by a cycle ergometer. Weight to the nearest 0.1 kg, height to the nearest 0.1 cm, and waist and hip circumferences were measured at the umbilical level and the greatest protruberance of the buttocks, respectively. The resting SBP and diastolic blood pressure (DBP) were determined three times following a 30-min rest period using a mercury sphygmomanometer, and the lowest values were used as their resting blood pressure. Graded exercise tests using a cycle ergometer (Monark Co. Ltd., Stockholm, Sweden) were performed to evaluate the cardiorespiratory fitness by a skilled-identical examiner. The heart rate, electro-cardiograms and blood pressure were all monitored and recorded during the test. The exercise intensity increased three or four times every 4-min until their heart rate reached 70% of the heart rate max or above. The maximal oxygen uptake ($\dot{V}O_2$max) was predicted by an Åstrand and Rhyming nomogram,[41] a modality that is generally used to predict the $\dot{V}O_2$max, which is regarded as an index of cardiovascular fitness. The sex steroid hormones measured included T, FT, estradiol (E_2), dehydroepiandrosterone-sulfate (DHEA-S), and SHBG. Lipid profile was measured in TC, HDL-c, and triglyceride (TG). The concentrations of TC and TG were determined by the enzyme method. The HDL-c was quantitated using the heparinmanganese precipitation method. Fasting insulin (FIRI) was measured by a radioimmunoassay using IRI kits (Pharmasia, Uppsala, Sweden). E_2, T, FT, and DHEA-S were measured by a radioimmunoassay technique using commercial kits (DPC, Los Angeles, CA). SHBG was measured by an immunoradiometric assay technique using a SHBG [^{125}I] assay kit (Farmous Daiagnostica, Oulunsalo, Finland). HOMA-IR, the index for insulin resistance, was calculated from the fasting blood glucose and insulin concentrations by the formula: HOMA-IR = FIRI (μU/mL) $\times$ fasting blood glucose (FBG) (mmol/L)/22.5.[42,43]

Using the WHO diagnosis criterion[11] (FBG $\geq$ 110 mg/dL and at least two of the following: waist-hip ratio (W/H) > 0.90; TG $\geq$ 150 mg/dL or HDL-c < 35 mg/dL; blood pressure $\geq$ 140/90 mm Hg) for MS, the participators were divided into an MS group and a non-MS group. The difference between MS group and non-MS group was compared by the unpaired t-test. Differences in anthropometry, glucose or lipid metabolism, blood pressure, cardiorespiratory fitness were assessed by one-way ANOVA with *post hoc* comparisons made using Fisher's PLSD test, in equally divided three tertiles of each sex steroid hormone index. Regarding the MS diagnosis as the dependent variable, logistic regression was performed to assess the odds ratios (ORs) and confidence interval (CI) of every level in every sex steroid hormone index. Age and SFA—the parameters that show difference in ANOVA tests in most indices—were added into the model as adjustment factors.

As the calculated FT (CFT) using T and SHBG values was recently reported to be more accurate than a radioimmunoassay-measured FT, we duplicated the analyses concerning FT using the CFT.

All data are presented as the mean ± SE and all statistical analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC). All p values were two-tailed, and statistical significance was defined as $p < 0.05$.

RESULTS

The subjects ranged in age from 20 to 64 years old. Teenagers and elderly men older than 64 were not enrolled in this study. The

anthropometric and metabolic characteristics of the 98 men are summarized in Table 1. According to the diagnosis criterion, 42 subjects were classified into the MS group, and 56 subjects were classified as non-MS. Compared with the non-MS group, the MS group had a significantly higher waist-to-hip ratio, resting blood pressure (both SBP and DBP), TC, TG, FBG, FIRI, HOMA-IR, VFA and SFA, but a significantly lower $\dot{V}O_2$max, HDL-C, SHBG, and T/E_2. The radioimmunoassay-measured FT (MS vs. non-MS: 16.23 ± 0.99 pg/mL vs. 16.10 ± 0.69 pg/mL) demonstrated different values than the CFT (MS vs. non-MS: 10.36 ± 0.43 ng/dL vs. 9.91 ± 0.38 ng/dL) in value. No significant difference was found in indices concerning FT or CFT between the two groups. Compared with the IGT group, the type 2 diabetes group had a significantly higher blood glucose indices, HOMA-IR, and the clustering of MS risk factors. No significant difference was found in age, W/H, blood pressure, $\dot{V}O_2$max, TC, HDL-C, TG, FIRI, VFA, SFA, or any sex steroid hormone indices.

Among sex steroid hormone indices, only E_2 ($r = 0.353$, $p = 0.0003$) and T/E_2 ($r = -0.241$, $p = 0.0165$), but not T ($r = -0.028$, $p = 0.7861$), FT ($r = 0.089$, $p = 0.3839$), CFT ($r = 0.154$, $p = 0.1305$), DHEA-S ($r = 0.082$, $p = 0.4226$), SHBG ($r = -0.188$, $p = 0.0636$), FT/E_2 ($r = -0.188$, $p = 0.0639$), or CFT/E_2 ($r = -0.196$, $p = 0.0533$), were significantly correlated with BMI.

Within each sex steroid hormone index, 98 patients were consecutively divided into three tertiles, high, medium or low, 31–34 patients in each tertile. Differences in anthropometry, glucose or lipid metabolism, blood pressure and cardiorespiratory fitness among tertiles of each index were assessed using one-way ANOVA tests. When ANOVA tests showed a significant difference, *post hoc* comparisons using Fisher's PLSD tests were additionally conducted. The comparison results are shown in Table 2. Age was significantly different among tertiles of SHBG or T/E_2. FIRI was different among tertiles of T/E_2. SFA was significantly different among tertiles of SHBG, T/E_2 or FT/E_2. No difference was found among tertiles of E_2 or T, and within FT and DHEA-S, only age showed a difference among the three tertiles (data not show).

In order to investigate the association between the sex steroid hormone index level and the prevalence of MS, multivariate logistic re-

TABLE 1. ANTHROPOMETRIC AND METABOLIC CHARACTERISTICS IN THE METABOLIC SYNDROME (MS) AND NON-METABOLIC SYNDROME (NON-MS) GROUPS

	MS (n = 42)	*non-MS (n = 56)*	*p*
Age (years)	49.21 ± 1.23	51.14 ± 1.13	0.2545
W/H	0.96 ± 0.01	0.93 ± 0.01	0.0101[a]
$\dot{V}O_2$max (mL/kg/min)	32.14 ± 0.69	35.92 ± 0.68	0.0002[a]
SBP (mm Hg)	135.31 ± 2.82	126.36 ± 1.89	0.0075[a]
DBP (mm Hg)	87.50 ± 1.82	80.04 ± 1.11	0.0004[a]
TC (mg/dL)	224.19 ± 5.52	209.16 ± 4.69	0.0401[a]
HDL-C (mg/dL)	45.19 ± 1.83	52.68 ± 1.70	0.0038[a]
TG (mg/dL)	200.86 ± 12.95	122.38 ± 10.18	<0.0001[a]
FBG (mg/dL)	151.81 ± 5.45	131.50 ± 4.33	0.0040[a]
FIRI (μU/mL)	8.19 ± 1.09	5.29 ± 0.35	0.0056[a]
HOMA-IR	3.21 ± 0.51	1.67 ± 0.10	0.0011[a]
VFA (cm^2)	185.68 ± 7.07	143.898 ± 6.863	<0.0001[a]
SFA (cm^2)	158.94 ± 10.93	132.27 ± 8.95	0.0600
E_2 (pg/mL)	26.33 ± 1.51	22.55 ± 1.47	0.0810
T (ng/dL)	437.88 ± 17.95	471.50 ± 17.40	0.1889
FT (pg/mL); CFT(ng/dL)	16.23 ± 0.99; 10.36 ± 0.43	16.10 ± 0.69; 9.91 ± 0.38	0.9126; 0.4314
DHEA-S (ng/mL)	1914.31 ± 142.13	1905.41 ± 117.13	0.9613
SHBG (nmol/L)	26.62 ± 1.78	34.20 ± 1.98	0.0071[a]
T/E_2	18.78 ± 1.25	25.92 ± 1.91	0.0045[a]
FT/E_2; CFT/E_2	0.69 ± 0.06; 0.45 ± 0.03	0.88 ± 0.07; 0.54 ± 0.04	0.0562; 0.0959

Values are the mean ± SE.
[a]Significantly different between MS and non-MS, $p < 0.05$.

TABLE 2. DIFFERENCE AMONG THE TERTILES OF EACH SEX STEROID HORMONE INDEX

	SHBG			*T/E_2*			*FT/E_2*		
	High	*Medium*	*Low*	*High*	*Medium*	*Low*	*High*	*Medium*	*Low*
Age	54.0 ± 1.2	52.0 ± 1.2	45.1 ± 1.4[a,b]	52.9 ± 1.1	51.2 ± 1.3	46.7 ± 1.7[a,b]	50.9 ± 1.4	49.8 ± 1.4	50.2 ± 1.6
W/H	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	1.0 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0
$\dot{V}O_2$max	35.0 ± 0.9	34.9 ± 1.1	33.1 ± 0.7	35.0 ± 0.9	35.1 ± 1.0	32.8 ± 0.8	36.0 ± 0.9	33.2 ± 0.9	33.6 ± 0.9
SBP	127.4 ± 2.7	131.7 ± 3.1	131.5 ± 3.0	125.9 ± 2.6	132.1 ± 2.9	132.9 ± 3.1	123.4 ± 2.4	136.3 ± 2.9[a]	130.9 ± 3.0
DBP	80.8 ± 1.5	83.0 ± 1.8	85.8 ± 2.1	81.3 ± 1.5	82.9 ± 1.8	85.6 ± 2.2	80.2 ± 1.7	86.8 ± 1.7[a]	82.8 ± 2.0
TC	204.9 ± 6.9	216.4 ± 6.4	225.2 ± 5.1	204.2 ± 6.1	230.9 ± 6.2[a]	212.4 ± 5.8[b]	208.1 ± 5.9	226.8 ± 5.5	211.8 ± 7.1
HDL-C	52.3 ± 2.6	46.8 ± 2.2	49.1 ± 2.0	52.2 ± 2.7	46.6 ± 1.9	49.5 ± 1.9	52.8 ± 2.5	46.9 ± 2.2	48.8 ± 2.0
TG	130.0 ± 14.7	159.3 ± 15.6	178.3 ± 15.3	148.5 ± 16.1	163.2 ± 15.0	156.8 ± 15.5	154.2 ± 15.9	167.2 ± 15.7	146.3 ± 14.9
FBG	132.6 ± 4.9	133.0 ± 5.2	154.1 ± 7.2[a,b]	141.0 ± 6.0	140.4 ± 6.2	139.1 ± 6.4	144.5 ± 7.9	142.6 ± 4.7	133.3 ± 5.2
FIRI	5.4 ± 1.1	6.4 ± 0.7	7.7 ± 0.8	5.9 ± 1.1	5.3 ± 0.4	8.3 ± 0.9[b]	5.7 ± 0.8	7.6 ± 1.2	6.3 ± 0.6
VFA	147.5 ± 10.6	165.0 ± 10.0	172.8 ± 6.7	151.5 ± 10.1	156.1 ± 7.0	178.5 ± 9.9	148.9 ± 8.6	168.9 ± 9.5	167.8 ± 9.5
SFA	129.3 ± 12.7	133.0 ± 9.0	167.4 ± 13.1[a,b]	122.7 ± 12.1	133.7 ± 7.4	176.0 ± 14.2[a,b]	117.8 ± 6.8	162.6 ± 16.3[a]	150.9 ± 10.2

[a]Significantly different from the high tertile of the same index.
[b]Significantly different from the medium tertile of the same index.

gression analyses using the following two models were performed: model 1, adjusted for age; and model 2, adjusted for age and SFA, the two parameters that showed differences in more than two sex steroid hormone indices based on the ANOVA tests.

The odds-ratios for the prevalence of MS calculated by the model 1 were significantly higher both in the low tertile of SHBG (OR, 4.59; 95% CI, 1.44–14.63), T/E_2 (OR, 3.29; 95% CI, 1.13–9.57), FT/E_2 (OR, 3.10; 95% CI, 1.07–8.97) and in the medium tertile of FT/E_2 (OR, 3.69; 95% CI, 1.29–10.61) than that in the high tertile of each index. After additionally adjusting for SFA in the model 2 (Fig. 1), the odds-ratios continued to be significantly higher in the low tertile of SHBG (OR, 4.60; 95% CI, 1.43–14.86) and in the medium tertile of FT/E_2 (OR, 3.28; 95% CI, 1.10–9.73) than that in the high tertile of each index. The odds-ratios of the low tertiles of T/E_2 (OR, 2.94; 95% CI, 0.98–8.75; $p = 0.053$) and FT/E_2 (OR, 2.82; 95% CI, 0.95–8.32; $p = 0.061$) had a borderline significance. The 90% CI of odds-ratios for the prevalence of MS calculated by model 2 showed significantly for low tertiles of T/E_2 (OR, 2.94; 90% CI, 1.17–7.34) and FT/E_2 (OR, 2.82; 90% CI, 1.13–6.99). No similar results were observed in T, FT, E_2, or DHEA-S. The percentage of IGT/type 2 DM was not significantly different among the three groups classified by SHBG (high, medium, low—11/22, 8/23, 8/23), T/E_2 (high, medium, low—10/24, 8/24, 9/23), or FT/E_2 (high, medium, low—11/22, 7/26, 9/23) level.

DISCUSSION

In this epidemiological study, the relative hypogonadism seen in Japanese adult men who were newly diagnosed with IGT or type 2 diabetes mellitus, which had not yet been treated by either any pharmaceutical therapy or behavior modifying intervention, was found to be strongly associated with the prevalence of MS. We have reported that regardless of visceral fat accumulation, cardiorespiratory fitness was associated with such individual factors as hyperinsulinemia and low HDL-c,[7] or the clustering of MS risk factors[8] in the same cohort. Among three tertiles of different sex hormone indices, visceral adiposity and cardiorespiratory fitness were not different from each other. Relative hypogonadism was found to be associated with the prevalence of MS independent of age and SFA. MS has been reported to be associated

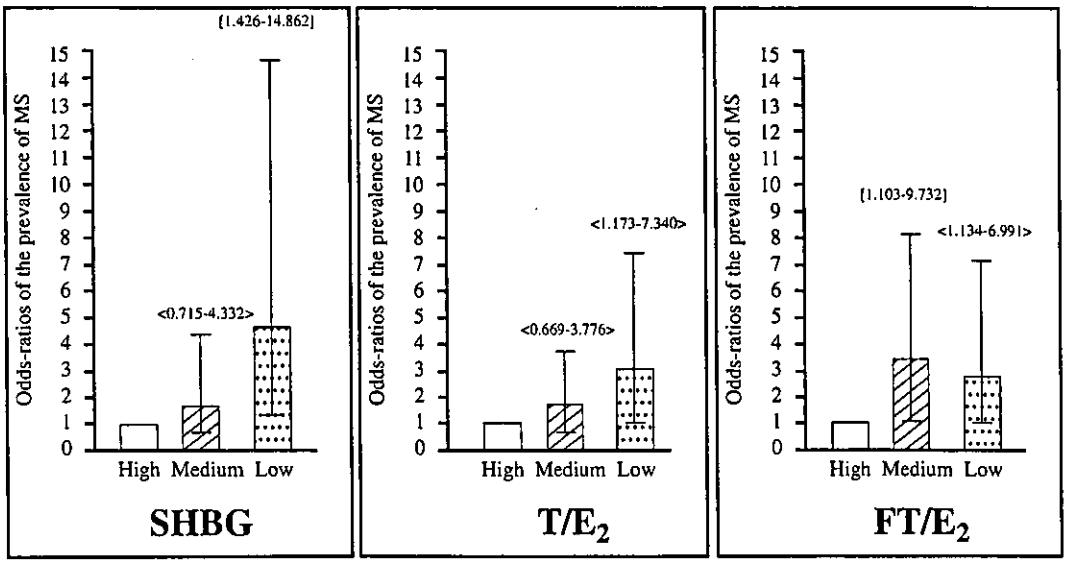

FIG. 1. Model 2. Odds-ratios of the prevalence of metabolic syndrome for each sex hormone tertile after adjusting for age and SFA. [#]; 95% CI; <#>: 90% CI.

with the development of type 2 diabetes[12,13] and relative hypogonadism was found in patients with type 2 diabetes.[18–21] The characteristic cohort here is ideal for verifying the contribution of the sex hormone index level to MS, and it also made it easier for us to investigate such interrelationships with less confounding. The subjects in this study had different pathological states such as IGT and type 2 diabetes. Compared with the IGT group, the type 2 diabetes group had a significantly higher blood glucose indices, HOMA-IR, and the clustering of MS risk factors. No significant difference was found in age, W/H, blood pressure, $\dot{V}O_2$max, TC, HDL-C, TG, FIRI, VFA, SFA, or any sex steroid hormone indices. The ratio of IGT/type 2 diabetes was not significantly different among the three groups classified by SHBG, T/E_2, or FT/E_2 level. We then interpreted that an adjustment for pathological state in the logistic regression model was not necessary.

Regarding the highest tertiles as criterion, lower SHBG, T/E_2 or FT/E_2 had a higher OR of prevalence of MS even after adjusting for age and SFA.

Sex steroid hormones have been reported to be important regulators of glucose and lipid metabolism. Lower levels of T or SHBG have been reported in men with type 2 diabetes.[18–21] Several prospective studies have shown that low levels of T and SHBG predict the development of type 2 diabetes in middle-aged men.[44,45] Hyperinsulinemia is associated with low concentrations of free and total T in men.[24,25]

Sex steroids modulate the action of insulin and influence body fat distribution by their effects on lipoprotein lipase (LPL) activity. The fasting adipose tissue LPL activity was found to correlate inversely with the plasma E_2 levels, consistent with E_2 being a negative regulator of adipose tissue LPL activity.[46] Such action of E_2 on the lipid metabolism therefore opposes that of insulin, whose effects on adipose tissue are anabolic, thus promoting energy storage. Androgens also play a role in the regulation of LPL activity. In a study by Iverius et al.,[46] the adipose tissue LPL activity positively correlated with the plasma FT levels, thus suggesting that T action is opposite that of E_2. A study of T substitution in hypogonadal male subjects showed a marked increase in LPL and the hepatic lipase activities.[47] This suggests that androgens play a physiological role in the regulation of triacylglycerol metabolism by maintaining the LPL activity and, like insulin, thus promoting anabolism.

Compared with lean controls, obesity in male patients is associated with relative hypogonadism.[25] Visceral obesity is believed to be associated more closely with insulin resistance than subcutaneous obesity does and abdominal obesity has been listed into the diagnosis criterion of MS. Visceral obesity is well recognized to be the characteristic for men as well as subcutaneous obesity for women. The administration of T in men reduced W/H[48] or visceral adiposity,[49,50] while it decreases the blood glucose level and improves insulin resistance,[48–50] thus suggesting that T plays a role in maintaining normal insulin resistance at physiological levels.[51] T replacement in men (or E_2 therapy in postmenopausal women) is known to decrease the visceral adipose tissue LPL activity.[50,52]

Relatively little is known regarding the influence of sex steroids on blood pressure. Both SBP and DBP significantly increase following the onset of menopause,[53–55] and the administration of E_2 to normotensive postmenopausal women tended to reduce the 24-h ambulatorily monitored blood pressure.[56–63] A lower level of circulating T has been reported in hypertensive men.[64–66] According to the data from Mårin et al.,[49,50] DBP decreased after T treatment in men. In view of the specific decrease of visceral fat mass in these studies, visceral adipose may mediate within the regulation of T on blood pressure. On the other hand, it was reported that T may elevate the blood pressure by altering the levels of endothelin-1[67] or catecholamines.[68]

MS is a syndrome consisting of a disturbed glucose and insulin metabolism, abdominal obesity, dyslipidemia, and hypertension. However, in the current study, rather than E_2, T or FT, which showed a relationship with individual component of MS, T/E_2 and FT/E_2, as well as SHBG, all showed a strong correlation with the incidence of MS, even after adjusting for age and SFA. Considering the fact that MS is a syndrome based on a disturbed glucose and

nsulin metabolism, the results in this study are in line with the finding that T/E_2 is associated with insulin in normal,[69,70] obese adult men,[35] or adult male patients with myocardial infarction[33] or coronary artery disease.[71] T/E_2 has also been reported to correlate more strongly than T with the insulin area, glucose area, and the ratio of insulin area-to-glucose area in the glucose tolerance test in non-obese men.[32] We duplicated the same statistical analyses used in the current study in a male cohort with normal glucose tolerance, SHBG but not FT/E_2 predicted the clustering of the MS risk factors (unpublished data). Therefore, in addition to SHBG, the balance of androgen and estrogen, rather than any individual sex hormones, plays an important role in the prevalence of abnormal glucose tolerance or MS in adult men.

There are some limitations in the current study. First, a part of the findings concerning FT in present study were based on the measurement of FT using a radioimmunoassay technique. This assay method of FT is still widely used in the worldwide[72] but has recently been reported to be inaccurate.[72–75] In view of this, we duplicated the same analysis using the CFT, an index calculated from T and SHBG concentrations which was reported to be reliable.[73] We duplicated the logistic regression analysis concerning FT/E_2 using the CFT. Unfortunately, although the CFT significantly correlated with the FT measured by direct assay ($r = 0.522$, $p < 0.0001$), and the odds-ratios calculated by the CFT showed a similar tendency (medium, 2.058; low, 1.456), the confidence interval of these odds-ratios (medium, 0.875–4.842; low, 0.614–3.454, 90%CI) were not statistically significant. Secondly, as cardiorespiratory fitness was indirectly determined, the accuracy of the determination might affect the result even in study made on such a scale. Thirdly, a cross-sectional model is not a powerful enough model to investigate the relationship between relative hypogonadism and the development of MS. We carried out a 1-year-last interventional to study the same relationship from a dynamic state. The results of the interventional study are expected to strengthen the findings reported herein.

In conclusion, in Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not accepted any pharmaceutical treatment or behavior rectifying intervention, lower T/E_2, FT/E_2, or SHBG, a relative hypogonadism status was found to be strongly associated with the prevalence of MS.

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地域在住高齢者の転倒発生への身体的・精神的要因の関与に関する前向き研究

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A PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN PHYSICAL DIFFICULTIES AND MENTAL PROBLEMS AND FALLS IN COMMUNITY-DWELLING ELDERLY.

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Abstract

The purposes of this prospective study were to investigate the incidence of falls or recurrent falls (more than 2 falls) and the falls-related risk factors, and to clarify the relationship between physical difficulties and mental problems and falls or recurrent falls in the elderly persons living independently in a local community in Japan. The participants were 775 elderly persons aged 60−79 years who participated in baseline assessment in 2002 by the questionnaire concerning the falls with injury during the past 5 years, and they had no injurious fall for 5 years before this survey. During prospective monitoring for 1 year, 173 falls were reported by 122 persons (15.7%), and recurrent falls were reported by 35 persons (4.5%). Significant gender difference was observed in falls for 1 year (Falls; men 11.3% vs female 20.0%, Recurrent falls; men 2.6% vs female 6.4%, $p<0.05$). Relationship between falls or recurrent falls and potential risk factors were identified in multiple logistic regression models. Physical difficulties (difficulties with standing from chair without their arms, balance on the one leg, and/or walking easily) was not associated with either falls. Mental problems (stressful, gloomy, less willingness, poor sleep, and/or forgetful) increased the risk of recurrent falls (Relative Ratio (RR) =3.50, 95% Confidence Interval (95%CI) =1.05-1.49). However, when physical difficulties were analyzed as a continuous variable, with each physical difficulty added, an relative ratio for recurrent falls increased by 1.5 times (95%CI=1.07-2.11) while mental problems did not show significant relation. When physical difficulties and mental problems were simultaneously analyzed, the risk of recurrent falls significantly increased in the category that had both physical difficulties and mental problems (RR=5.82, 95%CI= 1.25-27.04). These results suggest that mental treatments can be useful as a strategy for falls prevention in the elderly, as well as physical treatments.

Key Words: Falls, Elderly, Physical difficulties, Mental problems, Prospective study

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はじめに

高齢者の転倒は、寝たきりや転倒後症候群などを誘発することから、高齢期の身体的自立を脅かす要因であると考えられる。わが国における高齢者の年間転倒率は10-20%である[1-4]。これは欧米諸国に比べて低い発生率であるものの[5-7]、超高齢化に伴い転倒および転倒による諸問題は、本邦にあっても高齢者の深刻な健康問題として注目されている。転倒の予防には、まず転倒発生の要因を明らかにすることが重要である。欧米で行われた疫学研究によれば、転倒発生の危険因子として、高齢であること、女性であること、精神疾患薬の服用、身体の可動性の低下および認知障害などが報告されている[5-7]。特に身体能力の低下は転倒発生の重要な要因であることが示されている[8]。高齢期においては身体能力の低下だけでなく、抑うつなど精神心理的機能低下も生じる。地域高齢者を対象に抑うつと身体能力の低下との関連に焦点を当てた研究では、抑うつ症状または臨床的に診断された抑うつ双方は身体能力低下と密接に関連することが報告されている[9,10]。一方、身体能力低下が抑うつを増加させうるとの報告もあり[11]、両者には密接な関連性があることが示唆されている。

これまでに、身体能力の低下および抑うつは転倒発生の単独要因であることが報告されている[5-8,12]。すなわち、身体能力の低下と抑うつは相互に影響しあっていることから、両要因を併せ持つことは、単独要因に比べ相乗的もしくは相加的に転倒発生を高めることが予測される。しかしながら、先行研究において、この二要因の転倒発生に関する相互作用を検討した報告はない。我々[13]は、本研究に先立ち、ベースライン調査の横断的解析で、過去５年間の傷害を伴う転倒経験と身体的不自由および精神的不定愁訴との関連を検討した。その結果、二つの要因を併せ持つこと、さらにその数が増すほど転倒発生のオッズ比は有意に増加することを観察した。一般にある疾病や種々の健康事象の発生要因を証明しようとする場合、要因が結果に先行していること（関連の時間性）が要求される。すなわち、先述の我々の結果は、横断的調査における過去５年間の転倒経験の関連要因を明らかにしたに過ぎず、転倒の発生要因を明らかにしたとはいえない。そこで、本研究では地域在住の高齢者を対象として、転倒発生とその関連要因を明らかにし、転倒発生への身体的不自由および精神的不定愁訴の相互作用について、過去５年間に傷害を伴った転倒の未経験者を対象に１年間の前向き調査を実施したので報告する。

方法

１.対象者

本研究の対象者は、2002年に福岡県宗像郡津屋崎町在住の60歳以上の高齢者4,296名を対象として設定されたコホートの対象者である（Fig.1）。

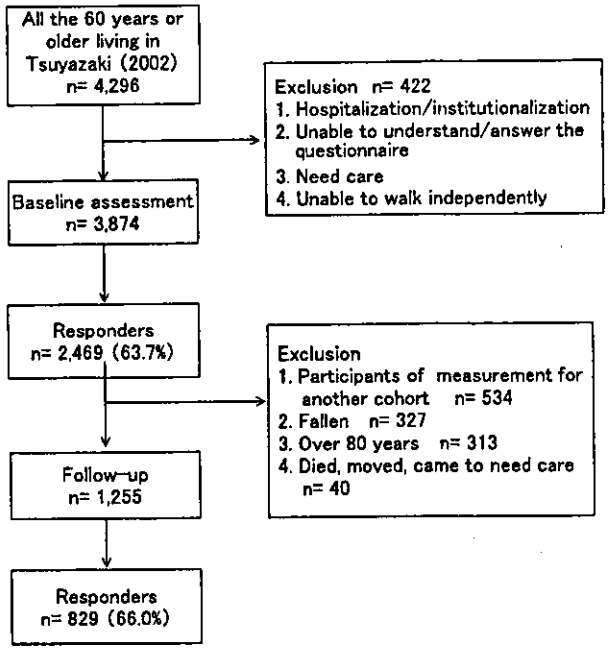

Fig.1 The flow chart of selection for participants in this study.

津屋崎町は、九州の北端、福岡市、北九州市両政令都市のほぼ中間に位置した人口約14,000人、60歳以上の人口割合27.2%（2002年）の町である。ベースライン調査は、自立している在宅高齢者を対象とするため、対象除外条件として①入所あるいは入院中であること、②精神疾患または理解不十分な者、③既に介護認定者であること、④自立歩行できないこと、以上４項目に当てはまる422名を除く3,874名であった。なお、対象者の除外条件適合の判定は、津屋崎町に16年勤務する保健師１名によって行われた。

2002年２月に実施したベースライン調査のデータは、郵送法によるアンケート調査から得られた。送付対象であった3,874名のうち80歳以上の対象者（529名）には、民生委員による個別訪問調査を実施した。最終的に2,507名から返信があり、そのうち有効回答者数は転倒経験に関する項目に回答した2,469名（63.7%）であった。対象者の内訳は、男性1,060名、女性1,409名であり、年齢はそれぞれ71.6±7.7歳、71.8±8.2歳であった。

このうち、別コホートの設定で体力測定を受けた554名、過去５年間に傷害を伴う転倒を経験した者327名、80歳