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 ($32 \leq \dot{V}O_{2max} < 36$ in men, $26 \leq \dot{V}O_{2max} < 30$ in women), and high-fit ($\dot{V}O_{2max} \geq 36$ in men, $\dot{V}O_{2max} \geq 30$ 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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Submitted June 27, 2003; accepted November 3, 2003.

Supported by grants for research project from the Japanese Association of Sports Medicine and Physical Fitness, and from the Institute of Health Science, Kyushu University and Chikushi Hospital, Fukuoka University.

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0026-0495/04/5305-0001$30.00/0
doi:10.1016/j.metabol.2003.11.023

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

ACKNOWLEDGMENT

We express our gratitude to all individuals who contributed to this study.

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