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Cardiorespiratory Fitness and Metabolic Markers in Healthy Young Adult Men

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Abstract. [Purpose] The purpose of this study was to clarify the relationship between cardiorespiratory fitness and metabolic markers, including leptin, in healthy young adults. [Subjects] The subjects were 51 healthy young men (mean age, 21.6 years; range, 18–31 years). [Methods] Ventilatory threshold and maximal oxygen uptake were measured on a cycle ergometer. The metabolic markers, HDL-cholesterol, triglyceride, fasting glucose, fasting insulin and leptin, were also measured, as well as and body composition, body height, body weight, percentage fat mass, waist circumference, and hip circumference. Blood pressure levels were recorded at rest. [Results] Our results show that lower cardiorespiratory fitness was significantly associated with higher storage of fat, lipid markers of developing atherosclerosis, and circulating leptin levels. Higher circulating leptin levels were also associated with metabolic risk markers such as obesity and insulin resistance. [Conclusion] Our results suggest that appropriate cardiorespiratory fitness may improve circulating metabolic markers even in healthy young men. It is therefore important that all persons should have high cardiorespiratory fitness from an early period of life for the effective prevention of cardiovascular disease.
Key words: Cardiorespiratory fitness, Leptin, Healthy young adults

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INTRODUCTION

Cardiorespiratory fitness and regular physical activity reduce the risk of cardiovascular diseases (CVD) and overall mortality in adults in general[1–3)]. Valuable indices of aerobic exercise intensity, ventilatory threshold (VT) and maximal oxygen uptake (VO_2max), are important predictors of cardiorespiratory fitness[4,5)]. Higher cardiorespiratory fitness is also related to higher physical activity and lower risk for CVD in asymptomatic Japanese elderly adults[6)]. Since VT and VO_2max decrease with aging[7,8)], cardiorespiratory fitness through greater physical activity should be acquired early in life to effectively prevent future events associated with CVD.

Obesity, glucose intolerance, dyslipidemia, and hypertension are well-known components of metabolic syndrome. All these conditions, characterized by insulin resistance, are associated with increased cardiovascular morbidity and mortality[9)]. Lower cardiorespiratory fitness and related low physical activity are frequently observed in subjects with metabolic syndrome[10,11)]. Lifestyle modifications such as appropriate dietary intake and physical exercise starting early in life definitely improve some of these CVD risk factors.

Recent studies have indicated that adipose tissue is a highly active endocrine organ secreting a range of hormones, which are likely to act as mediators between body fat distribution and insulin sensitivity[12)]. Of these hormones, leptin is an adipocyte-derived hormone that regulates energy balance, metabolism, and the neuroendocrine response to alter nutritional status[13)]. Leptin also prevents triglyceride synthesis and insulin resistance, repartitioning fatty acids toward oxidation and away from storage of tissue[14)]. However, body fat mass is independently associated with circulating leptin levels[16)] and most obese populations show resistance to the actions

of this versatile hormone[14]. Hyperleptinemia in obese subjects is associated with hyperphagia, insulin resistance, dyslipidemia, and hypertension[15], as well as an increased risk of clinical CVD[17]. Several recent studies have shown that cardiorespiratory fitness is negatively correlated with leptin levels[15], and that regular physical training for obese men reduced body fat mass and metabolic markers, while improving leptin levels and insulin sensitivity to appropriate levels[18]. Little is yet known, however, as to what specific interaction exists between aerobic fitness and leptin in healthy young adults[15].

In the present study, we evaluated the relationship between cardiorespiratory fitness and metabolic markers, including leptin, in order to shed light on their effects on the cardiorespiratory fitness in healthy young adults.

SUBJECTS AND METHODS

Subjects

Prior to the study, approval was obtained from the Special Medical Research Ethics Committee of Nagasaki University (project registration number 07022837). After obtaining their informed consent, we enrolled 51 healthy young adult men (mean age, 21.6 years; range, 18–31 years). None of the participants had apparent past or present histories of diabetes mellitus or atherosclerosis-related disease (cerebral infarction / hemorrhage or ischemic heart disease).

Methods

Venous blood samples were collected from each subject after a 12-h overnight fast. Serum and plasma were separated on site and stored at –80°C until assayed. High-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were measured by enzymatic methods (Daiichi Chemical, Tokyo, Japan). Fasting glucose (FG) was measured by the hexokinase method (Shino Test, Tokyo, Japan), and fasting insulin (FI) by a chemiluminescence immunoassay (Kyowa Medix, Tokyo, Japan). The homeostasis model assessment for insulin resistance (HOMA-R) was calculated as FI (μU/mL)*FG (mg/dL)/405[19]. Concentrations of serum leptin were determined with a radio-immunoassay (HUMAN LEPTIN RIA KIT; Linco Research Inc., St. Charles, Missouri, USA).

Body weight and percentage body fat (PBF) were measured using a body composition analyzer (DC-320; Tanita Co. Ltd, Tokyo, Japan) with impedance methods after overnight fasting. Body height was measured to the nearest 0.1 cm using a height bar fixed on a wall. The body mass index (BMI) was calculated as body weight (kg) divided by body height squared (m^2). Waist circumference (WAC) and hip circumference (HIC) were measured with a flexible tape measure to the nearest 0.1 cm, and the waist-to-hip ratio (WHR) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at rest.

To determine the aerobic capacity of each subject, gas exchange during an exercise test was measured on a cycle ergometer Aerobike 75XL II® (Conbi Wellness Co. Ltd, Nagoya, Japan) with a compact metabolic analyzer VO2000® (Medical Graphics, St. Paul, Minnesota, USA). The test protocol was a ramp exercise test (25 watt/min) after a 3-min, 25-watt warm-up. The test was terminated when the target heart rate was reached (80% of the predicted maximum heart rate: 220 – age in years). Oxygen uptake (VO_2), carbon dioxide output (VCO_2), and heart rate were recorded using m-graph v1.9 software® (S&ME Inc, Tokyo, Japan). The heart rate and VO_2 data obtained in the exercise test were plotted and extrapolated to the estimated maximal heart rate, and predicted VO_2max. VT estimated by gas exchange was determined using the V-slope method[20].

The obtained data are expressed as mean ± standard deviation or the median with the 25th and 75th percentiles. Since the values of TG, TG/HDL-C, FI, HOMA-R, and leptin were distributed in a skewed manner, logarithmic transformation was done before performing multiple linear regression analysis, which was performed to identify predictors of VT, VO_2max and leptin adjusted for age. Probability values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS v11.0 software (SPSS Japan, Tokyo, Japan).

Table 1. Characteristics of the study subjects

		Range (min– max)
Subjects (n)	51	
Age (years)	21.6 ± 3.1	18 – 31
BMI (kg/m^2)	21.0 ± 2.4	16.5 – 29.1
PBF (%)	16.0 ± 4.8	7.5 – 29.4
WAC (cm)	74.9 ± 6.5	62.8 – 95.9
HIC (cm)	92.4 ± 5.4	84.4 – 108.6
HDL-C (g/L)	0.60 ± 0.10	0.39 – 0.87
TG (g/L)	0.52 (0.44–0.80)	0.24 – 2.51
TG/HDL-C	0.86 (0.63–1.41)	0.43 – 6.44
FG (g/L)	0.85 ± 0.05	0.76 – 0.98
FI (mU/L)	4.2 (3.2–5.6)	1.3 – 23.3
HOMA-R	0.90 (0.67–1.12)	0.27 – 5.64
Leptin (μg/L)	1.4 (0.8–2.2)	0.5 – 12.7
SBP (mmHg)	114.0 ± 8.6	96 – 135
DBP (mmHg)	68.9 ± 7.2	56 – 91
VT (mL/kg/min)	18.9 ± 4.0	11.7 – 28.1
VO_2max (mL/kg/min)	43.8 ± 6.8	26.9 – 59

Values are mean ± standard deviation or median (25th – 75th quartile). BMI indicates body mass index; PBF, percentage body fat; WAC, waist circumference; HIC, hip circumference; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; HOMA-R, homoeostasis model assessment for insulin resistance; FG, fasting glucose; FI, fasting insulin; SBP, systolic blood pressure; DBP, diastolic blood pressure; VT, ventilatory threshold; VO_2max, maximal oxygen uptake.

RESULTS

The characteristics of the 51 subjects are shown in Table 1. BMI and clinical markers of metabolic syndrome of the subjects fell within near-normal ranges. Simple correlation analysis showed that VT was significantly correlated with age ($r=-0.29$, $p<0.05$), but VO_2max was not correlated with age ($r=0.20$, $p=0.17$). Multiple linear

Table 2. Multiple linear regression analysis of VT and VO_2max adjusted for age

	VT (mL/kg/min)		VO_2max (mL/kg/min)	
	β	95%CI	*β*	95%CI
BMI (kg/m^2)	–0.18	–0.759, 0.177	–0.14	–1.234, 0.451
PBF (%)	–0.32	–0.498, –0.035*	–0.25	–0.779, 0.068
WAC (cm)	–0.29	–0.351, –0.001*	–0.38	–0.701, –0.092*
HIC (cm)	–0.32	–0.441, –0.030*	–0.42	–0.878, –0.164*
HDL-C (g/L)	0.23	–1.398, 19.59	–0.08	–24.58, 13.97
TG (g/L)	–0.26	–10.86, 0.229	–0.07	–12.65, 7.875
TG/HDL-C	–0.29	–9.418, –0.374*	–0.04	–9.538, 7.392
FG (g/L)	–0.09	–29.43, 14.69	–0.002	–39.81, 39.39
FI (mU/L)	–0.17	–7.631, 2.101	0.09	–6.222, 11.34
HOMA–R	–0.18	–7.637, 1.722	0.09	–6.057, 10.89
Leptin (μg/L)	–0.35	–8.333, –0.940*	–0.34	–14.46, –1.155*
SBP (mmHg)	–0.12	–0.186, 0.072	–0.09	–0.302, 0.162
DBP (mmHg)	–0.10	–0.208, 0.099	–0.03	–0.300, 0.252

Multiple linear regression analysis was performed to identify predictors of VT and VO_2max adjusted for age. The standard regression coefficient (β) is the average amount such that the dependent variable increases when the independent variable increases by one unit while other variables are held constant. Confidence interval (CI) of 95% represents the plus/minus range around the observed sample regression coefficients. If the coefficient interval includes 0, then there exists no significant linear relationship. * $p<0.05$.

regression analysis adjusted for age indicated VT was significantly related to PBF (β= –0.32, $p<0.05$), WAC (β= –0.29, $p<0.05$), HIC (β= –0.32, $p<0.05$), TG/HDL-C (β= –0.29, $p<0.05$), and leptin (β= –0.35, $p<0.05$) (Table 2). The same analysis also indicated that VO_2max was significantly related to WAC (β= –0.38, $p<0.05$), HIC (β= –0.42, $p<0.05$), and leptin (β= –0.34, $p<0.05$) (Table 2).

Simple correlation analysis showed that leptin was significantly correlated with age ($r=0.36$, $p<0.05$). Multiple linear regression analysis adjusted for age indicated that leptin was significantly related to BMI (β=0.61, $p<0.05$), PBF (β=0.77, $p<0.05$), WAC (β=0.63, $p<0.05$), HIC (β=0.59, $p<0.05$), HDL-C (β= –0.27, $p<0.05$), TG (β=0.36, $p<0.05$), TG/HDL-C (β=0.39, $p<0.05$), FI (β=0.36, $p<0.05$), HOMA-R (β=0.35, $p<0.05$), SBP (β=0.28, $p<0.05$), and DBP (β=0.29, $p<0.05$) (Table 3).

Table3. Multiple linear regression analysis of leptin adjusted for age

	leptin (μg/L)	
	β	95%CI
BMI (kg/m^2)	0.61	0.048, 0.103*
PBF (%)	0.77	0.037, 0.060*
WAC (cm)	0.63	0.019, 0.040*
HIC (cm)	0.59	0.020, 0.046*
HDL-C (g/L)	–0.27	–1.549, –0.018*
TG (g/L)	0.36	0.163, 0.949*
TG/HDL-C	0.39	0.182, 0.819*
FG (g/L)	0.20	–0.428, 2.771
FI (mU/L)	0.36	0.111, 0.790*
HOMA-R	0.35	0.106, 0.761*
SBP (mmHg)	0.28	0.001, 0.019*
DBP (mmHg)	0.29	0.001, 0.023*

Multiple linear regression analysis was performed to identify predictors of leptin adjusted for age. The standard regression coefficient (β) is the average amount such that the dependent variable increases when the independent variable increases by one unit while other variables are held constant. Confidence interval (CI) of 95% represents the plus/minus range around the observed sample regression coefficients. If the coefficient interval includes 0, then there exists no significant linear relationship. * $p<0.05$.

DISCUSSION

Recent studies have shown that VT and VO_2max decrease with aging[7,8], and that they are negatively correlated with visceral fat area, abdominal subcutaneous fat area and WAC in adults[21–23]. In this study, we showed that VT is negatively related to PBF, whereas VT and VO_2max are negatively related to WAC and HIC, but not to BMI in healthy young adults. These results suggest that the cardiorespiratory fitness of healthy young adults is influenced not by the volume of skeletal muscle but rather by storage of fat, inclusive of visceral and abdominal subcutaneous fat.

The results indicate that VT is negatively related to TG/HDL-C in healthy young adults. The V-slope method showed that changes in the VCO_2/VO_2 ratio were due to aerobic and anaerobic metabolism with increasing intensity. V-slope consists of two linear slopes, i.e., a lower slope that reflects aerobic metabolism and an upper slope reflecting both aerobic and anaerobic metabolism[20]. Exercises below the VT circulating free fatty acids are consumed by aerobic metabolism in skeletal muscles. Weight loss after aerobic exercise training has been shown to be modest, but it facilitate body fat loss[24]. TG/HDL-C is used as a measure of dyslipidemia since the combination of high TG and low HDL-C levels characterizes "Syndrome X"[25]. TG/HDL-C has also been associated with the presence of atherogenic

small dense LDL particles[26]. High affinities of small dense LDL for arterial proteoglycans, or other cell surface sites, may enhance the trapping of small dense LDL, prompting modification of the vascular wall, which are both processes known tocontribute to the development of atherosclerosis[27]. Ichihara et al.[6] reported that a higher cardiorespiratory fitness level was associated with higher physical activity and lower CVD risk factors, i.e., lower TG and higher HDL-C, in asymptomatic middle-aged adults. Our present study demonstrated that a higher capacity of aerobic metabolism in exercise may routinely induce an increase in circulating lipids even in healthy young adults.

VT and VO_2max were found to be negatively related to circulating leptin levels in healthy young adults. Leptin regulates expenditure of skeletal muscle[28], and obesity is characterized by hyperleptinemia and leptin resistance in the hypothalamus and peripheral tissues in the general population[27]. A stepwise multiple regression analysis in our study showed that circulating leptin levels were an independent determinant of VT (β=–0.41, $p<0.05$) and VO_2max (β=–0.33, $p<0.05$) when age, PBF, TG/HDL-C, and leptin were included as independent values (data not shown). This suggests that cardiorespiratory fitness may be associated with circulating leptin levels in healthy young adults.

The concentration of circulating leptin is an independent determinant of HOMA-R in healthy young adults, and a recent study showed that leptin promoted glucose uptake and fatty acid oxidation in skeletal muscles by activation of AMPK, with peripheral influence on skeletal muscle and sympathetic nerves from the center[28]. Storage of TG in skeletal muscle, which consumes free-circulating fatty acids, inhibits glucose uptake and fatty acid oxidation, and it may increase insulin resistance[14]. Also, physical exercise improves leptin levels and insulin sensitivity to appropriate levels, and the quantities of these changes correlate with each other[18,29]. Our results suggest that increased circulating leptin levels might also be partly associated with insulin resistance even in healthy young adults. Higher circulating leptin levels were also associated with higher SBP and DBP. In elderly adults, dyslipidemia with obesity results in elevation of blood pressure levels through sympathetic nerve activation by leptin[30]. Our present results suggest that leptin may slowly influence blood pressure levels, even in a young population, such as the one used in this study.

There were several limitations to this study. Our study sample size was relatively small and included only men. Due to the cross-sectional design of our study, it is hard to determine to what extent the findings reflect the cause and effect phenomenon.

In conclusion, we showed that lower cardiorespiratory fitness was significantly associated with higher PBF and circulating leptin levels and TG/HDL-C, a lipid marker of developing atherosclerosis. Additionally, higher circulating leptin levels were associated with higher insulin resistance and blood pressure levels even in healthy young adults. The results suggest that appropriate cardiorespiratory fitness may improve circulating lipid profiles in healthy young men. We also showed that circulating leptin levels may influence insulin sensitivity and blood pressure in young men. Having higher cardiorespiratory fitness from an early period in life may be important for the prevention of CVD. Further attempts to identify risk factors and to develop screening methods for the evaluation of risk markers that are related to cardiorespiratory fitness will be needed for the establishment of effective strategies for preventing CVD that can be adopted at an early stage of life.

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