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SHORT COMMUNICATION

Circulating leptin levels are associated with physical activity or physical fitness in Japanese

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Abstract

Objective The aim of this study was to evaluate the link between circulating leptin levels and physical activity and/or physical fitness in apparently healthy Japanese.

Methods A total of 85 men and 111 women who were not taking any medication were enrolled in this cross-sectional study. Circulating leptin levels, physical activity measured by tri-axial accelerometers and peak oxygen uptake were evaluated. We also assessed anthropometric data, blood pressure, blood examinations and energy intake.

Results Circulating leptin levels were 3.2 ± 2.3 ng/mL in men and 5.9 ± 3.8 ng/mL in women. Circulating leptin levels were significantly and positively correlated with body weight, body mass index, abdominal circumference, insulin and the homeostasis model assessment index, and significantly and negatively correlated with peak oxygen uptake in both sexes. Stepwise multiple regression showed that peak oxygen uptake in men and physical activity evaluated by $\sum$[metabolic equivalents × h per week (METs h/w)] in women were determinant factors for circulating leptin levels after adjusting for confounding factors.

Keywords Leptin · Japanese · Physical activity · Peak oxygen uptake · Tri-axial accelerometer

Introduction

Leptin [1] is primarily expressed by adipose tissue and is one of the major adipocytokines. Recombinant leptin reduces food intake and body weight in both human and mouse models through its effect on the central nervous system [2–4]. In addition, in clinical practice, circulating leptin levels are positively associated with the damage to the arterial walls, obesity, type 2 diabetes mellitus and metabolic syndrome risk factors in both young people and adults [5–8].

It is well known that physical activity and/or physical fitness are closely linked to metabolic disorders [9–11]. Sawada et al. [12] reported that a low cardiorespiratory fitness level is an important risk factor for incidence of type 2 diabetes among Japanese men by prospective cohort study. Sandvik et al. [13] also showed that physical fitness was a graded, independent, long-term predictor of mortality due to cardiovascular causes in healthy, middle-aged men. Taken together, physical activity and/or physical fitness may reduce circulating leptin levels. In fact, we have also showed that exercise education and using pedometer significantly reduced serum leptin levels for up to 1 year of follow-up [14].

Some studies in the literature have reported a relation between circulating leptin levels and physical activity and/or physical fitness [15–21]. However, neither the link between accurately evaluated circulating leptin levels and physical activity and/or physical fitness nor the combined effect of physical activity and/or physical fitness on circulating leptin levels has not been fully discussed in

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Table 1 Clinical characteristics of the enrolled subjects

	Men			Women		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Number of subjects	85			111		
Age (years)	44.0 ± 9.7	30	64	46.4 ± 8.7	30	64
Height (cm)	169.5 ± 5.4	157.3	181.0	158.0 ± 5.3	148.2	174.5
Body weight (kg)	66.6 ± 8.4	49.9	105.3	54.1 ± 8.0	35.3	76.4
Body mass index (kg/m^2)	23.1 ± 2.7	18.2	34.3	21.6 ± 3.0	13.2	31.3
Abdominal circumference (cm)	81.8 ± 8.0	68.5	110.8	77.1 ± 8.9	61.5	104.3
Peak oxygen uptake (mL/kg/min)	38.1 ± 8.0	16.5	55.8	29.5 ± 5.9	15.0	45.2
Physical activity (METs h/w)	23.4 ± 15.4	1.19	74.1	23.4 ± 12.5	3.5	66.4
Systolic blood pressure (mmHg)	125.0 ± 12.1	101.0	159.0	115.2 ± 12.8	92.0	162.0
Diastolic blood pressure (mmHg)	77.6 ± 8.1	59.0	94.0	70.3 ± 9.6	52.0	96.0
Blood profile						
Leptin (ng/mL)	3.2 ± 2.3	0.5	14.7	5.9 ± 3.8	1.0	20.6
Triglyceride (mg/dL)	106.1 ± 74.4	34.0	554.0	74.0 ± 35.2	29.0	200.0
HDL cholesterol (mg/dL)	60.4 ± 18.3	30.0	149.0	69.2 ± 12.8	41.0	103.0
Blood glucose (mg/dL)	94.0 ± 11.3	73.0	146.0	88.3 ± 8.3	59.0	133.0
Insulin(μU/mL)	5.3 ± 3.6	0.9	22.6	4.8 ± 2.7	0.6	16.5
HOMA index	1.3 ± 1.2	0.2	7.9	1.1 ± 0.7	0.1	4.0
Energy intake (kcal)	2111.1 ± 467.7	1013.4	3536.0	1663.0 ± 424.7	686.0	3383.3
Number of subjects with smoking habit (%)	20 (23.5)			1 (0.9)		

METs h/w, Σ [metabolic equivalents × h per week (METs h/w)]; HOMA index, homeostasis model assessment index

apparently healthy Japanese. In addition, the simple effect of physical activity and/or physical fitness without metabolic disorders on circulating leptin levels is needed to be investigated. Therefore, in this cross-sectional study, we evaluated the relationship between circulating leptin levels and physical activity and/or physical fitness in apparently healthy Japanese who were thought to have lower insulin resistance.

Methods

Subjects

We used data for 196 subjects (85 men and 111 women) among 1,118 subjects originally enrolled at Okayama Southern Institute of Health, Okayama Health Foundation, Okayama, Japan (256 subjects) and the National Institute of Health and Nutrition, Tokyo, Japan (862 subjects) who met the following criteria: (1) wanted to enroll in the Nutrition and Exercise Intervention Study (NEXIS) at Okayama Southern Institute of Health; (2) had been tested for anthropometric data, physical activity, peak oxygen uptake, blood pressure (BP) measurements and blood examinations including circulating leptin levels; (3) received no medication such as drugs for diabetes, hypertension, or dyslipidemia; and (4) provided written informed consent (Table 1).

Ethical approval for the study was obtained from the Ethical Committee of the Okayama Health Foundation, Okayama, Japan and the National Institute of Health and Nutrition, Tokyo, Japan. This original study protocol was registered in the ClinicalTrials.gov Identifier (NCT00926744).

Blood sampling and assays

After the subjects fasted and rested overnight for 10–12 h, blood samples were collected to determine circulating levels of leptin, high-density lipoprotein (HDL) cholesterol, triglycerides (L Type Wako Triglyceride·H, Wako Chemical, Osaka, Japan), blood glucose and insulin. Circulating leptin levels were measured using a HUMAN LEPTIN RIA (LINCO Research, Inc., USA). Blood glucose was measured by the glucose-oxidant method. Serum insulin was measured by chemiluminescent immunoassay (CLIA) (ABOTT Japan Co. LTD., Tokyo, Japan). Plasma glucose was measured using the glucose-oxidant method. The insulin resistance was evaluated using the homeostasis model assessment (the HOMA index) [fasting plasma glucose (mg/ dl) × fasting serum insulin (μU/ml)/405], according to the method developed by Matthews et al. [22].

Clinical parameters

Anthropometric parameters, physical activity measured using a tri-axis accelerometer, peak oxygen uptake, systolic BP (SBP), diastolic BP (DBP), cigarette smoking habit and energy intake according to a comprehensive brief-type self-administered diet history questionnaire (BDHQ) were evaluated as previously described [23] in the NEXIS Study.

Statistical analysis

All data are expressed as mean ± SD values. Pearson's correlation coefficients were calculated and used to test the significance of the linear relationship between continuous parameters, where $p < 0.05$ was considered statistically significant. Stepwise multiple regression analysis was also performed to test the relationship between circulating leptin levels and other clinical variables.

Results

The clinical parameters of the enrolled subjects are summarized in Table 1. Circulating leptin levels were 3.2 ± 2.3 ng/mL in men and 5.9 ± 3.8 ng/mL in women. Physical activity over 3 METs per week evaluated by a tri-axis accelerometer was 23.4 ± 15.4 METs h/w in men and 23.4 ± 12.5 METs h/w in women. Peak oxygen uptake was 38.1 ± 8.0 mL/kg/min in men and 29.5 ± 5.9 mL/kg/min in women (Table 1).

We evaluated the relationship between circulating leptin levels and clinical parameters (Table 2). Circulating leptin levels were significantly and positively correlated with body weight, BMI, abdominal circumference, insulin and the HOMA index in both sexes. Circulating leptin levels were significantly and negatively correlated with peak oxygen uptake in both sexes. In addition, weak relationships between circulating leptin levels and triglycerides or blood glucose in both sexes were noted. There were also weak relationships between circulating leptin levels and HDL cholesterol in men, and between circulating leptin levels and SBP and physical activity evaluated by $\sum[\text{metabolic equivalents} \times \text{h per week}(\text{METs h/w})]$ in women.

Finally, we used stepwise multiple regression analysis to evaluate the effect of clinical parameters, i.e., age, BMI, abdominal circumference, energy intake [24], cigarette smoking, physical activity and peak oxygen uptake on circulating leptin levels, and found that BMI, abdominal circumference, age and peak oxygen uptake were significant in men [Circulating leptin levels $= -6.115 + 0.259$ (BMI) $+ 0.109$ (abdominal circumference)-0.050 (age)$-$0.089 (peak oxygen uptake), $r^2 = 0.714$, $p < 0.0001$]. Meanwhile, BMI, abdominal circumference and physical activity (METs h/w) were significant in women [Circulating leptin levels $= -15.979 + 0.650$ (BMI) $+ 0.114$ (abdominal circumference)-0.043 (physical activity), $r^2 = 0.613$, $p < 0.0001$].

Discussion

In this study, we first evaluated the relationship between circulating leptin levels and physical fitness and/or physical activity using a tri-axial accelerometer in apparently healthy Japanese. Stepwise multiple regression analysis showed that peak oxygen uptake in men and physical activity in women were closely associated with circulating leptin levels even after adjusting for confounding factors.

Leptin-deficient ob/ob mice have decreased activity [25] and pharmacological therapy with leptin increased activity and decreased adiposity [25]. Leptin receptor-deficient db/db mice also showed hypoactivity [26]. Murakami et al. [27] investigated the relationship between Q223R polymorphism in the leptin receptor (LEPR) gene and physical activity level, and showed that RR genotype of Q223R polymorphism in the LEPR gene was associated with shorter time spent in light physical activity and longer inactive time in free-living Japanese. In clinical study, Martinez-Gomez et al. [15] reported that vigorous physical activity evaluated by accelerometer for 7 days and cardiorespiratory fitness were inversely associated with leptin in 198 adolescents. Jimenez-Pavon et al. [16] also showed that physical activity and fitness testing were negatively correlated with leptin. Breaks in sedentary time were significantly inversely associated with leptin [17]. However, Franks et al. [18] showed that leptin was significantly associated with physical activity energy expenditure, but not with cardiorespiratory fitness. Higher total or central fat mass was the only predictor of higher plasma leptin, and no other variables, i.e., physical activity energy expenditure and physical fitness added any power to predict [19]. In addition, in some reports, leptin was negatively correlated with maximal oxygen uptake only in men [20, 21]. Therefore, the results of the relationship between circulating leptin levels and physical activity and/or physical fitness varied.

In this study, we accurately evaluated the relationship between circulating leptin levels and physical activity using a tri-axial accelerometer and/or physical fitness in apparently healthy Japanese assumed to be without insulin resistance. Stepwise multiple regression analysis showed that peak oxygen uptake in men and physical activity in women were predictors for circulating leptin levels, as well as BMI and abdominal circumference. The difference in physical fitness and circulating leptin levels between men

Table 2 Simple correlation analysis between serum leptin levels and clinical parameters

	Men		Women	
	r	*p*	*r*	*p*
Age (years)	0.028	0.8004	0.072	0.4511
Height (cm)	0.025	0.8231	0.004	0.9702
Body weight (kg)	0.714	**<0.0001**	0.700	**<0.0001**
Body mass index (kg/m^2)	0.754	**<0.0001**	0.746	**<0.0001**
Abdominal circumference (cm)	0.799	**<0.0001**	0.712	**<0.0001**
Peak oxygen uptake (mL/kg/min)	−0.571	**<0.0001**	−0.470	**<0.0001**
Physical activity (METs h/w)	−0.213	0.0509	−0.251	**0.0079**
Systolic blood pressure (mmHg)	0.196	0.0718	0.201	**0.0348**
Diastolic blood pressure (mmHg)	0.057	0.6038	0.176	0.0645
Blood profile				
Triglyceride (mg/dL)	0.368	**0.0005**	0.365	**<0.0001**
HDL cholesterol (mg/dL)	−0.289	**0.0074**	−0.138	0.1483
Blood glucose (mg/dL)	0.356	**0.0008**	0.378	**<0.0001**
Insulin(μU/mL)	0.521	**<0.0001**	0.636	**<0.0001**
HOMA index	0.486	**<0.0001**	0.650	**<0.0001**
Energy intake (kcal)	−0.010	0.9277	−0.078	0.4173

Bold values indicate statistical significance ($p < 0.05$)

METs h/w, Σ [metabolic equivalents × h per week (METs h/w)]; HOMA index, homeostasis model assessment index

and women may have caused the gender difference in this study. In fact, circulating leptin levels in women were higher than those in men, while peak oxygen uptake in men was higher than that in women. Moro et al. [28] reported that overweight women mobilize more lipids, as assessed by glycerol, than men during exercise, and that the exercise-induced increase in plasma catecholamine levels was lower in women compared with men. Nevertheless, the findings of this study suggest that the effect of physical activity and/or physical fitness on circulating leptin levels is independent of body composition in subjects with lower insulin resistance.

There are some potential limitations in this study. First, our study was cross-sectional rather than longitudinal, so the effects of long-term physical activity and/or physical fitness could not be evaluated clearly. Second, 196 subjects in our study voluntarily underwent measurements: they were, therefore, more likely to be health conscious than an average person. Third, we could not explain the gender difference or a clear mechanism between circulating leptin levels and physical activity and/or physical fitness. In addition to the differences of circulating leptin levels and peak oxygen uptake, sex differences of leptin secretion have shown using adipocytes. Adipocytes in women secreted significantly higher amounts of leptin than those in men by dexamethasone- and estradiol-stimulated conditions [21, 29], suggesting differential regulation of leptin between men and women. However, it seems reasonable to suggest that promoting physical fitness in men and physical activity in women will result in reduced circulating leptin levels in clinical practice. To confirm these findings, ongoing studies are required in the Japanese population.

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Conflict of interest The authors declare no conflict of interest.

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