

# UC Irvine

## UC Irvine Previously Published Works

### Title

The relationships between leptin and measures of fitness and fatness are dependent upon obesity status in youth.

### Permalink

<https://escholarship.org/uc/item/0hk772qs>

### Journal

Pediatric Exercise Science, 22(2)

### ISSN

0899-8493

### Authors

Hosick, Peter A  
McMurray, Robert G  
Cooper, Dan M

### Publication Date

2010-05-01

### DOI

10.1123/pes.22.2.195

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at

<https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

# The Relationships Between Leptin and Measures of Fitness and Fatness Are Dependent Upon Obesity Status in Youth

**Peter A. Hosick and Robert G. McMurray**  
University of North Carolina at Chapel Hill

**Dan M. Cooper**  
University of California, Irvine

The relationship between peak aerobic fitness (peak $\text{VO}_2$ ) and plasma leptin was assessed in 25 normal (BMI < 85th %tile) and 25 overweight (BMI > 85th %tile) youth, ages 7–17 years. In the overall analysis peak $\text{VO}_2$  was related to leptin when expressed in mL/kg/min ( $R^2 = .516$ ,  $p < .0001$ ), or as mL/kg $_{\text{FFM}}$ /min ( $R^2 = .127$ ,  $p = .01$ ). The relationships between peak $\text{VO}_2$  and leptin were no longer significant when percent bodyfat was added to the models. In subanalyses by weight groups, peak $\text{VO}_2$ : leptin relationships were not evident for normal weight, but remained for overweight youth. In conclusion the relationship between aerobic fitness and leptin in youth is dependent upon weight status.

Leptin is a hormone produced by adipose tissue and is involved in satiety cues and energy expenditure (14). Plasma leptin concentration is positively correlated to level of adiposity (5,14); with females having higher circulating levels than males (9,11). Besides adiposity, leptin influences, or maybe influenced by, a number of different factors including gender, age, the endocrine system, and aerobic fitness (20). However, confusion exists in our current understanding of the relationship between leptin and aerobic fitness ( $\text{VO}_{2\text{max}}$ ). Cross-sectional studies in adults have shown a moderate relationship between leptin and aerobic fitness, expressed as either mL $\text{O}_2$ /kg/min or  $\text{LO}_2$ /min. Conversely, longitudinal studies have noted that changes in aerobic fitness without change in weight do not always result in changes in leptin (22). If there is a direct relationship between leptin and aerobic fitness, then one would expect that a change in aerobic fitness should consistently result in a change in leptin.

Little research has been completed on the relationship between leptin and aerobic fitness in youth. Gutin et al. (16) have shown in overweight youth that physical training reduced leptin levels, even after adjustment for reduction in fatness. McMurray et al. (25), using a cross-sectional study of adolescents, have shown

---

Hosick and McMurray are with the Dept. of EXSS, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-8700. Cooper is with the Pediatric Exercise Research Center, Dept. of Pediatrics, University Children's Hospital, University of California, Irvine, Irvine, CA.

that plasma leptin concentration is associated with aerobic fitness ( $\text{VO}_2\text{max}$ , ml/kg/min). However, in children and adolescents genetics is an important predictor of aerobic fitness (3) and body fat content (18). Thus, when there is an increase or decrease of adipose tissue, the interaction of leptin with aerobic fitness can be modified (2,10,30,31). Thus, further clarification is needed regarding the relationship between leptin and aerobic fitness.

The confusion in the relationship between leptin and aerobic fitness could be related to the units of measure used for aerobic fitness. The most commonly reported unit is milliliters of oxygen per kilogram body mass per minute (mL/kg/min). However, ml/kg/min includes both fat free (FFM) and fat mass, yet fat as the site of leptin production (29). Aerobic fitness can also be reported in the absolute measurement of milliliters of oxygen per minute (mL/min). This unit of analysis is confounded by the fact that larger or overweight individuals typically have increased muscle mass in addition to extra adipose tissue. This increased muscle mass results in a larger absolute oxygen uptake. What is needed is a means of expressing aerobic fitness independent of fat mass, such as oxygen uptake per kilogram fat free mass ( $\text{ml/kg}_{\text{FFM}}/\text{min}$ ). Therefore, the purpose of this investigation is to examine the relationship between plasma leptin concentration and aerobic fitness in a sample of normal and overweight adolescents, while taking body fat and fat free mass into consideration.

## Methods

### Subjects

Subjects consisted of 50 adolescents that ranged in age from seven to 17 years. The University of California at Irvine institutional review board approved the study with all of the subjects being recruited from the local community. Written informed consent was obtained from the participant and the participant's legal guardian before participating in the study. Subjects with history of any chronic medical conditions or chronic use of any medications were excluded from participation. The entirety of the data collection was carried out at the General Clinical Research Center at the University of California-Irvine Medical Center. Complete subject characteristics appear in Table 1.

### Anthropometric Measurements

Standard, calibrated scales and stadiometers were used to determine height and body mass, for calculating BMI ( $\text{kg}/\text{m}^2$ ). Since BMI changes with age during normal development in children and adolescents, BMI percentile (BMI%tile) for each subject was obtained using the published standards from the Centers for Disease Control and Prevention, National Center for Health Statistics (27). In addition, body fat content and fat free mass were assessed using a dual-energy x-ray absorptiometry; DEXA, (Hologic QDR 4500 Densitometer, Hologic, Inc., Bedford MA). Subjects were scanned in light clothing while lying flat on their backs. DEXA scans were performed and analyzed using pediatric software. On each day of testing, the DEXA instrument was calibrated according to the manufacturer's specifications.

**Table 1 Mean  $\pm$  SD Characteristics of the Subjects Presented by Weight Group**

	Overall $n = 50$	Normal $n = 25$	Overweight $n = 25$
Male/Female	24/26	13/12	11/14
Height (cm)	156.8 $\pm$ 13.4	157.0 $\pm$ 14.5	156.6 $\pm$ 12.6
Weight (kg)	70.0 $\pm$ 23.6	46.9 $\pm$ 12.9	75.1 $\pm$ 23.6*
Age (y)	12.5 $\pm$ 2.5	12.8 $\pm$ 2.4	12.1 $\pm$ 2.6
BMI (kg/m <sup>2</sup> )	24.3 $\pm$ 7.5	18.6 $\pm$ 2.2	30.0 $\pm$ 6.5*
BMI percentile	71.4 $\pm$ 30.4	45.6 $\pm$ 22.0	97.3 $\pm$ 2.4*
Body Fat (%)	31.1 $\pm$ 12.0	21.1 $\pm$ 6.3	41.1 $\pm$ 18.8*
VO <sub>2</sub> (mL/min)	1628 $\pm$ 550	1574 $\pm$ 648	1682 $\pm$ 437
VO <sub>2</sub> (kg/ml/min)	28.3 $\pm$ 8.6	33.2 $\pm$ 7.4	23.5 $\pm$ 7.0*
VO <sub>2</sub> (ml/kg <sub>FFM</sub> /min)	41.0 $\pm$ 8.6	42.4 $\pm$ 6.7	39.6 $\pm$ 10.0
Leptin (ng/ml)	24.0 $\pm$ 22.3	6.6 $\pm$ 6.0	41.3 $\pm$ 18.8*

\*significantly different from normal at  $p \leq 0.05$

Note. BMI = body mass index.

## Aerobic Fitness Measures

Each subject performed a progressive exercise test to volitional fatigue on a cycle ergometer to obtain peak oxygen uptake (6). All subjects received vigorous external motivation from the staff during high-intensity phases of the exercise protocol and claimed volitional fatigue at the end of the test at which point peak heart rate and respiratory exchange ratio (RER) were recorded and blood sample taken to measure lactate. However, as with most maximal testing in youth not all subject met at least 3 criteria for a maximal test; therefore, the tests were deemed to be peakVO<sub>2</sub> tests (peakVO<sub>2</sub>) rather than VO<sub>2</sub>max tests. Gas exchange was measured breath-by-breath using a Sensor Medics metabolic system (Yorba Linda, CA). PeakVO<sub>2</sub> was calculated in units of milliliters per minute (VO<sub>2</sub>mL/min), milliliters per kilogram body mass per minute (VO<sub>2</sub>ml/kg/min) and ml per kilogram fat free mass per minute (VO<sub>2</sub>ml/kg<sub>FFM</sub>/min).

## Blood Sampling

All blood sampling occurred on a separate visit from the fitness trial. The children were instructed not to participate in high-intensity prolonged exercise within 24 hr of the visit and were not to eat for at least 3 hr before arrival. Blood was sampled using an indwelling catheter placed in the antecubital vein. All blood samples were immediately cold-centrifuged and with plasma decanted and frozen at -80 °C for later analysis. Resting plasma leptin concentration was determined on all samples using the commercially available Human Leptin kit (Linco, St. Louis, MO).

## Data Management and Analysis

Mean and standard deviations for all subjects were computed for all variables. Bivariate correlations between resting leptin and BMI %tile, percent fat (%fat), fat free mass (FFM) and peakVO<sub>2</sub> were computed for the overall sample and by weight group. Stepwise multiple regression models using all subjects were used to determine the influences of aerobic fitness, percent bodyfat and fat-free mass. Percent body fat was used in the models rather than fat mass because of the high collinearity between fat mass and fat free mass ( $r = .52$ ;  $p < .0001$ ), whereas there was no significant collinearity between percent fat and FFM ( $p > .44$ ). These analyses were completed for two different units of aerobic fitness (mL/kg/min or mL/kg<sub>FFM</sub>/min). Because of a lack of significance between it and resting leptin, mL/min was omitted from further analysis. The models were developed in iterations with the first being only aerobic fitness, the second included aerobic fitness and percent body fat, and the third included the previous two variables and FFM. All models additionally included sex, to account for differences in leptin and aerobic fitness, and age, to account for age-related differences in power.

A scatterplot was then developed with leptin and BMI percentile. Visually, this plot suggested that the relationship between leptin and fat was linear for subjects with a BMI < 85th %tile. The relationship appeared exponential for subjects with a BMI > 85th %tile. For this reason the sample was also divided into two weight group based on BMI percentile. Those with >85th BMI %tiles were considered overweight and those <85th BMI %tile were considered normal weight. Means and standard deviations were computed within weight groups and *t* tests were used to compare descriptive data between normal and overweight adolescents. Bivariate correlations between leptin and BMI %tile, %fat and FFM were previously defined, FFM and peakVO<sub>2</sub> were computed by weight group. The relationships of leptin to aerobic fitness and fatness were then reexamined within weight groups using the same regression models as above. All models were adjusted for sex to account for differences in leptin and fitness (21) and age to account for age-related differences in fitness (1). The alpha level for statistical significance was set at  $p \leq .05$  and SAS statistical software (SAS, Cary, NC, USA) were used for all analyses.

## Results

The mean data ( $\pm SD$ ) for all subjects combined and separated by weight group (normal and overweight) are displayed in Table 1. Combined mean ( $\pm SD$ ) for peak heart, lactate and RER were  $177 \pm 14$  bpm,  $5.6 \pm 2.9$  mmol/L and  $1.08 \pm 0.02$ , respectfully. The age and height distribution between the two weight groups were similar. Body mass, BMI, BMI%tile, %fat and resting leptin were significantly greater in the overweight subjects. Peak aerobic fitness, expressed as (mL/kg/min) was significantly lower in the overweight group. However, when peakVO<sub>2</sub> was expressed as (mL/kg<sub>FFM</sub>/min) there was no difference between normal and overweight adolescents.

The bivariate correlations (Table 2) between resting leptin and body composition or peakVO<sub>2</sub> are presented in Table 2. With the overall sample, correlations between leptin and all variables were significant; the lowest was between leptin and FFM while the highest was between leptin and %fat. When weight groups were

**Table 2 Correlations Between Leptin and Body Composition Measures and PeakVO<sub>2</sub>**

Leptin	Combined	Overweight	Normal
BMI%	0.728*	0.731*	0.297
% fat	0.884*	0.782*	0.591*
FFM	0.297*	0.275	-0.19
Fat Mass	0.857*	0.686*	0.492*
VO <sub>2</sub> (mL/min)	0.032	0.061	-0.423*
VO <sub>2</sub> (mL/kg/min)	-0.718*	-0.574*	-0.708*
VO <sub>2</sub> (mL/kg <sub>FFM</sub> /min)	-0.356*	-0.332	-0.604*

\* $p \leq .05$

separated, the majority of the correlations remained significant for the overweight group, with the exception of FFM. For the normal weight group %fat, fat mass, and the three measures of peakVO<sub>2</sub> were significantly related; whereas BMI %tile and FFM were not significantly related.

The stepwise multiple regression models overall and by weight group for the associations between leptin, peak VO<sub>2</sub> and measures of body comp are included in Table 3 and 4. In the first iteration of the overall model aerobic fitness expressed in units of mL/kg/min had a moderate the  $R^2 = .516$  (Table 3). When %fat was added to the model, the total  $R^2$  increased with %fat contributing the majority of the variance, while the amount of variance contributed by peakVO<sub>2</sub> was no longer significant ( $p > .15$ ). In the third iteration FFM was not a significant contributor. Similar analyses for peakVO<sub>2</sub> in terms of mL/kg<sub>FFM</sub>/min resulted in peakVO<sub>2</sub> having an  $R^2 = .127$ ;  $p = .01$  (Table 4). When %fat was added to the model the  $R^2$  for peakVO<sub>2</sub> was reduced and no longer significant. As above, %fat was the main contributor, while FFM did not contribute significantly.

Because the relationship between leptin and aerobic fitness was different between weight groups, the regression analyses were then computed within weight groups, accounting for sex and age. Normal weight subjects had a small, but significant, amount of the variance in leptin explained by peakVO<sub>2</sub> expressed in units of mL/kg/min ( $R^2 = .090$ ). In the second and third iterations the addition of %fat and FFM did not significantly explain any further amount of variance, with the majority of the reported  $R^2$  being explained by age and sex. The overweight group had a greater amount of variance attributed to peakVO<sub>2</sub> than the normal weight group. In these overweight subjects the second and third iterations resulted in both %fat and FFM contributing significantly. Furthermore, when these body composition characteristics were added, the proportion of variance accounted for by peakVO<sub>2</sub> was reduced from  $R^2 = .330$  to  $R^2 = .047$ .

When peakVO<sub>2</sub> was expressed as mL/kg<sub>FFM</sub>/min, it did not significantly contribute to the variance for the normal weight group (Table 4). The addition of %fat or FFM did not contribute to the additional iterations of the regression analyses. In the overweight subjects little variance explained by peakVO<sub>2</sub> ( $R^2 = .111$ ;  $p = .10$ ) and the contribution was even less when %fat and FFM were added to the models.

**Table 3 Results of Stepwise Multiple Regression Analysis for the Association Between Resting Leptin, and VO<sub>2</sub> (ml/kg/min) (1st Iteration), Added %Fat (2nd Iteration) and Added FFM (3rd Iteration) Presented with Subjects Combined and Separately for Normal vs. Overweight Youth. Analysis Adjusted for Age and Sex**

#	Model	Combined		Normal		Overweight	
		Partial R <sup>2</sup>	p value	Partial R <sup>2</sup>	p value	Partial R <sup>2</sup>	p value
1	VO <sub>2</sub>	0.516	0.0001	0.090	0.04	0.330	0.003
	Total	0.516		0.646		0.330	
2	VO <sub>2</sub>	NS		0.090	0.04	0.047	0.05
	%fat	0.781	0.0001	NS		0.611	0.0001
	Total	0.824		0.646		0.765	
3	VO <sub>2</sub>	NS		0.090	0.04	0.047	0.05
	%fat	0.781	0.001	NS		0.611	0.0001
	FFM	NS		NS		0.040	0.05
	Total	0.824		0.646		0.0805	

NS = p value > 0.15

**Table 4 Results of Stepwise Multiple Regression Analysis for the Association Between Resting Leptin, and VO<sub>2</sub> (ml/kg<sub>FFM</sub>/min) (1st Iteration) Added %Fat (2nd Iteration) and Added FFM (3rd Iteration) Presented with Subjects Combined and Separately for Normal vs. Overweight Youth. Analysis Adjusted for Age and Sex**

#	Model	Combined		Normal		Overweight	
		Partial R <sup>2</sup>	p value	Partial R <sup>2</sup>	p value	Partial R <sup>2</sup>	p value
1	VO <sub>2</sub>	0.127	0.01	NS		0.111	0.10
	Total R <sup>2</sup>	0.127	0.01	NS		0.111	0.10
2	VO <sub>2</sub>	0.078	0.15	0.060	0.10	0.035	0.10
	%fat	0.781	0.0001	NS		0.611	0.0001
	Total R <sup>2</sup>	0.832		0.607		0.753	0.10
3	VO <sub>2</sub>	0.008	0.15	0.060	0.10	0.035	0.10
	%fat	0.781	0.0001	NS		0.611	0.0001
	FFM	NS		NS		0.042	0.06
	Total R <sup>2</sup>	0.832		0.607		0.795	

NS = p value > 0.15

## Discussion

This investigation attempted to clarify the separate and combined associations between leptin and aerobic fitness, %fat or FFM. The overall results indicated that when fat is accounted for, peakVO<sub>2</sub>, regardless of units, is not significantly related to leptin. Since %fat is the strongest predictor of resting leptin, this result was anticipated. However, these relationships changed when the analyses were completed within weight groups. In normal weight individuals peakVO<sub>2</sub> expressed as ml/kg<sub>FFM</sub>/min or ml/kg/min was more closely associated with leptin than body fat. This finding is supported by Ischander et al. (19), who found that in adolescent girls of equal body mass, those that had increased aerobic fitness (ml/kg/min) had decreased leptin. Conversely, in our overweight group, no relationship between peakVO<sub>2</sub> and leptin was evident, suggesting that their high amounts of fat mass appear to override any relationship between leptin and peakVO<sub>2</sub>. The elevated leptin and loss of leptin sensitivity of the overweight youth may only return to normal functioning when fat mass is reduced (5,13), or physical activity level is significantly increased, as Gutin et al. (16) have shown that an increase in activity can promote a decrease in resting leptin independent of fat mass changes.

The results of the correlations suggest that regardless of weight status, as %fat increases, resting leptin level increases. However, a dichotomy occurred when the relationship between leptin and FFM was examined, as a *positive* relationship was found between leptin and FFM in the overweight subjects, but a *negative* relationship was found between these two variables in the normal weight subjects. This follows because the overweight subjects not only have a higher body fat, but also had approximately 17% more FFM. Thus, the positive association between FFM and leptin may actually be indirectly related to the increased fat mass of the overweight subject requiring more FFM to support and move that greater fat mass.

Interestingly, when peakVO<sub>2</sub> was expressed as a function of total body mass (kg) normal weight subjects had significantly higher peakVO<sub>2</sub> than overweight subjects. However, when peakVO<sub>2</sub> was expressed as a function of FFM significant differences between the groups disappeared, but the mean values for the normal weight youth were still somewhat higher than the overweight youth (p~0.2). There are three possible interpretations for this result. First, taken at face value, the lack of significant difference suggests that the maximal metabolic capacity of active muscle tissue is similar between overweight and normal individuals. If so, then leptin may not have an active role in energy production or expenditure during acute bouts of exercise. Then little relationship between leptin and the aerobic fitness would be expected. This explanation seems most plausible, since we were not able to find any previous studies implying that leptin can have an acute effect on muscle metabolism.

An alternative argument could be made that the ~3 mL/kg<sub>FFM</sub>/min lower mean peakVO<sub>2</sub> (ml/kg<sub>FFM</sub>/min) of the overweight youth represented a real, but subtle difference, but with only 25 subjects in each group we were unable to find statistical significances. The reason that the small difference could be real is related to potential endocrine differences between normal and overweight people (4,10,23,24,26,31). The sympathetic nervous system (SNS) response to exercise appears to be higher in overweight individuals (20,33), yet the β-adrenergic activity



is decreased (28). This results in a decrease in catecholamine release (24) and lipolytic activity (12), which may play an acute role in altered muscle metabolism of overweight persons. Concomitantly, McMurray and Hackney have reported that obesity reduces the thyroid, growth hormone, cortisol and catecholamine responses to exercise (24). Since these hormones are involved with muscle development in youth and leptin interacts with them (24), chronic exposure to exercise in an obese child may not result in the same metabolic adaptations that occur in normal weight youth. Therefore, any reduction in peak  $\text{VO}_2$  ( $\text{ml}/\text{kg}_{\text{FFM}}/\text{min}$ ) may be related to the differences in the metabolic capacity of the muscle. This argument is somewhat complicated by the fact that an a posteriori power calculation indicated that an additional 20 subjects in each group would be needed to produce significant differences ( $\alpha=0.05$ ;  $\beta=0.80$ ).

Finally, both aerobic fitness and fatness have a genetic component. In adolescents body morphology and composition have genetic links (3,7,18) which can extend to leptin production and sensitivity. But aerobic fitness and fatness are altered to a degree by lifestyle choices, e.g., physical activity and food choices. Thus, genetics may have an underlying role, which can be modified by lifestyle.

The present article is not without limitations. The comparison of leptin value to peak  $\text{VO}_2$  relies heavily on accurate assessment of these parameters. That being said, we would like to acknowledge that not all the subjects met the minimum requirements for a successful maximal test. However, all subjects were verbally encouraged to exercise as long as possible and did complete a graded exercise test in which they claimed volitional fatigue upon completion. In addition, blood samples for leptin were obtained after a minimum of 3 hr fast; whereas leptin has been shown to be elevated for up to 8 hr postprandial (8). This may have resulted in slightly elevated resting leptin values in both overweight and normal groups. However, our leptin levels were within normal limits of what has been reported in similar investigations (17,34). Therefore, we do not believe this is a major confounder to the associations made within this investigation.

The results highlight the importance of separating individuals according to weight status when assessing the relationship between aerobic fitness and leptin. In normal weight youth resting leptin is related to peak  $\text{VO}_2$ , expressed either as a function of total body mass (kg) or fat free body mass (FFM). However, this is not the case for overweight youth. The most salient factor for these overweight youth is body fat content. Furthermore, any relationship that exists between leptin and peak  $\text{VO}_2$  in overweight subjects is likely due to the increased fat mass compounded with their greater FFM. In conclusion, the relationship between fitness, fatness and adipocyte-originated factors, such as leptin, in normal and overweight adolescents is different. In an attempt to account for these differences we recommend that aerobic fitness be expressed in units that adjust for body fat ( $\text{ml}/\text{kg}_{\text{FFM}}/\text{min}$ ). If aerobic fitness cannot be adjusted then any analysis should account for body fat, avoiding the colinearity between the units of aerobic fitness and body fat mass, using units like %fat, waist circumference or waist:height ratio, rather than body mass index or absolute kg of body fat.

## References

1. Armstrong, N., and J.R. Welsman. Assessment and interpretation of aerobic fitness in children and adolescents. *Exerc. Sport Sci. Rev.* 22:435–476, 1994.

2. Baratta, M. Leptin—from a signal of adiposity to a hormonal mediator in peripheral tissues. *Med. Sci. Monit.* 8:RA282–RA292, 2002.
3. Birrer, R.B., and R. Levine. Performance parameters in children and adolescent athletes. *Sports Med.* 4:211–227, 1987.
4. Cohen, B., D. Novick, and M. Rubinstein. Modulation of insulin activities by leptin. *Science.* 274:1185–1188, 1996.
5. Considine, R.V., M.K. Sinha, M.L. Heiman, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N. Engl. J. Med.* 334:292–295, 1996.
6. Cooper, D.M., D. Weiler-Ravell, B.J. Whipp, and K. Wasserman. Aerobic parameters of exercise as a function of body size during growth in children. *J. Appl. Physiol.* 56:628–634, 1984.
7. Czerwinski, S.A., M. Lee, A.C. Choh, et al. Genetic factors in physical growth and development and their relationship to subsequent health outcomes. *Am. J. Hum. Biol.* 19:684–691, 2007.
8. Dallongeville, J., B. Hecquet, P. Lebel, et al. Short term response of circulating leptin to feeding and fasting in man: influence of circadian cycle. *Int. J. Obes. Relat. Metab. Disord.* 22:728–733, 1998.
9. de Courten, M., P. Zimmet, A. Hodge, et al. Hyperleptinaemia: the missing link in the, metabolic syndrome? *Diabet. Med.* 14:200–208, 1997.
10. De Pergola, G. The adipose tissue metabolism: role of testosterone and dehydroepiandrosterone. *Int. J. Obes. Relat. Metab. Disord.* 24(Suppl. 2):S59–S63, 2000.
11. Ellis, K.J., and M. Nicolson. Leptin levels and body fatness in children: effects of gender, ethnicity, and sexual development. *Pediatr. Res.* 42:484–488, 1997.
12. Florkowski, C.M., G.R. Collier, P.Z. Zimmet, J.H. Livesey, E.A. Espiner, and R.A. Donald. Low-dose growth hormone replacement lowers plasma leptin and fat stores without affecting body mass index in adults with growth hormone deficiency. *Clin. Endocrinol. (Oxf.)* 45:769–773, 1996.
13. Frederich, R.C., A. Hamann, S. Anderson, B. Lollmann, B.B. Lowell, and J.S. Flier. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat. Med.* 1:1311–1314, 1995.
14. Friedman, J.M. Leptin, leptin receptors and the control of body weight. *Eur. J. Med. Res.* 2:7–13, 1997.
15. Friedman, J.M., and J.L. Halaas. Leptin and the regulation of body weight in mammals. *Nature.* 395:763–770, 1998.
16. Gutin, B., L. Ramsey, P. Barbeau, et al. Plasma leptin concentrations in obese children: changes during 4-mo periods with and without physical training. *Am. J. Clin. Nutr.* 69:388–394, 1999.
17. Hassink, S.G., D.V. Sheslow, E. de Lancey, I. Opentanova, R.V. Considine, and J.F. Caro. Serum leptin in children with obesity: relationship to gender and development. *Pediatrics.* 98:201–203, 1996.
18. Herbert, A. The fat tail of obesity as told by the genome. *Curr. Opin. Clin. Nutr. Metab. Care.* 11:366–370, 2008.
19. Ischander, M., F. Zaldivar, Jr., A. Eliakim, et al. Physical activity, growth, and inflammatory mediators in BMI-matched female adolescents. *Med. Sci. Sports Exerc.* 39:1131–1138, 2007.
20. Jones, P.P., K.P. Davy, S. Alexander, and D.R. Seals. Age-related increase in muscle sympathetic nerve activity is associated with abdominal adiposity. *Am. J. Physiol.* 272:E976–E980, 1997.
21. Kirel, B., N. Dogruel, N. Akgun, F.S. Kilic, N. Tekin, and B. Ucar. Serum leptin levels during childhood and adolescence: relationship with age, sex, adiposity and puberty. *Turk. J. Pediatr.* 41:447–455, 1999.
22. Lowndes, J., R.F. Zoeller, J.D. Caplan, et al. Leptin responses to long-term cardiorespiratory exercise training without concomitant weight loss: a prospective study. *J Sports Med Phys Fitness.* 48:391–397, 2008.

23. Mansoub, S., M.K. Chan, and K. Adeli. Gap analysis of pediatric reference intervals for risk biomarkers of cardiovascular disease and the metabolic syndrome. *Clin. Biochem.* 39:569–587, 2006.
24. McMurray, R.G., and A.C. Hackney. Interactions of metabolic hormones, adipose tissue and exercise. *Sports Med.* 35:393–412, 2005.
25. McMurray, R.G., J.S. Harrell, and S.A. Brown. Circulating leptin concentrations are not related to physical activity levels in adolescents. *Clin. Exerc. Physiol.* 2:159–164, 2000.
26. McMurray, R.G., F. Zaldivar, P. Galassetti, et al. Cellular immunity and inflammatory mediator responses to intense exercise in overweight children and adolescents. *J. Investig. Med.* 55:120–129, 2007.
27. Morrow, J.R., and P.S. Freedson. Relationship between habitual physical activity and aerobic fitness in adolescents. *Pediatr. Exerc. Sci.* 6:315–329, 1994.
28. Rayner, D.V., and P. Trayhurn. Regulation of leptin production: sympathetic nervous system interactions. *J. Mol. Med.* 79:8–20, 2001.
29. Ryan, A.S., and D. Elahi. The effects of acute hyperglycemia and hyperinsulinemia on plasma leptin levels: its relationships with body fat, visceral adiposity, and age in women. *J. Clin. Endocrinol. Metab.* 81:4433–4438, 1996.
30. Seals, D., and C. Bell. Chronic sympathetic activation: consequence and cause of age-associated obesity. *Diabetes.* 53:276–285, 2004.
31. Simsch, C., W. Lormes, K.G. Petersen, et al. Training intensity influences leptin and thyroid hormones in highly trained rowers. *Int. J. Sports Med.* 23:422–427, 2002.
32. Trayhurn, P., N. Hoggard, J.G. Mercer, and D.V. Rayner. Leptin: fundamental aspects. *Int. J. Obes. Relat. Metab. Disord.* 23(Suppl. 1):22–28, 1999.
33. Troisi, R.J., S.T. Weiss, D.R. Parker, D. Sparrow, J.B. Young, and L. Landsberg. Relation of obesity and diet to sympathetic nervous system activity. *Hypertension.* 17:669–677, 1991.
34. Vettor, R., G. De Pergola, C. Pagano, et al. Gender differences in serum leptin in obese people: relationships with testosterone, body fat distribution and insulin sensitivity. *Eur. J. Clin. Invest.* 27:1016–1024, 1997.