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Physical activity is correlated with serum leptin independent of obesity: results of the national surveillance of risk factors of noncommunicable diseases in Iran (SuRFNCD-2007)

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Abstract

Reports on the relationship between leptin and physical activity (PA) at the population level are scarce. The present study examined the relationship between serum leptin concentrations and PA in a nationally representative sample of 3001 Iranian adults aged 25 to 64 years. Data of our third national surveillance of risk factors of noncommunicable diseases were analyzed. Using the Global Physical Activity Questionnaire, the duration and intensity of PA were evaluated in 3 domains: work, commuting, and recreation. Total PA was calculated using metabolic equivalents for PA intensity. Serum leptin was measured with an enzyme-linked immunosorbent assay. After adjustment for age, area of residence, smoking, body mass index, and waist circumference, total PA ($r = -0.129$, $P = .038$ in men and $r = -0.226$, $P = .006$ in women), the duration of vigorous-intensity activity ($r = -0.120$, $P = .044$ in men and $r = -0.154$, $P = .019$ in women), the duration of moderate-intensity activity ($r = -0.114$, $P = .047$ in men and $r = -0.160$, $P = .018$ in women), and time spent on sedentary behaviors ($r = 0.194$, $P = .014$ in men and $r = -0.204$, $P = .007$ in women) were significantly correlated with serum leptin. In both sexes, participants in higher categories of PA had significantly lower serum leptin levels. In conclusion, our results demonstrated an inverse association between leptin concentrations and PA independent of age, sex, smoking, and body adiposity. Our results point to the regulatory effects of PA on serum leptin.

1. Introduction

Leptin has become a hot topic for obesity research since the discovery of a mutation in the mouse leptin gene that increased the animals' appetite while lowering their metabolic rate. However, novel findings decrease the prospect that this circulating signal may explain differences in body fat among people. Although there is a high degree of correlation between total adiposity and leptin levels, there is considerable interindividual variability in this relationship [1,2]; and many people with normal levels of leptin are overweight or obese. The mechanisms underlying this variability are unclear. Some individuals seem to be less sensitive to the modulating effects of leptin on adiposity or other modifiable metabolic parameters such as maximum oxygen uptake and physical activity energy expenditure (PAEE) [3-13].

In this context, it is important to know the association between serum leptin and different features of physical activity (PA). Evidence supporting an independent association between PA and leptin level is inconsistent [3-13]. This is due to the small number of studies on the subject and the

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imprecise measurement of energy expenditure. The latter is likely to be the result of the difficulties faced in accurately measuring PAEE in free-living populations.

Based on the data set of our third national surveillance of risk factors of noncommunicable diseases (SuRFNCD-2007), we recently reported the association between PA, insulin resistance, and metabolic syndrome [14,15]. In this study, we aimed to evaluate for the first time the association between serum leptin and different features of PA in a large nationally representative sample of Iranian adults.

2. Methods

2.1. Participants

This study was based on the data of our third SuRFNCD conducted in 2007. Details of the survey have been reported elsewhere [16]. In brief, a cluster sampling scheme was applied to randomly select a representative sample of Iranian adults aged 25 to 64 years. Each cluster comprised 2 men and 2 women in each age category (25-34, 35-44, 45-54, and 55-64 years). The number of clusters selected from each province was proportional to the urban/rural size of that province. For example, 51 clusters (1020 participants) were taken from Tehran (the largest province of Iran) and only 2 (40 participants) from Ilam (the smallest of the 30 provinces of Iran). Trained health care professionals conducted household interviews and physical examinations. All interviews were in Persian. The data were recorded in standardized questionnaires and were rechecked based on a predetermined schedule. Blood sampling was done within a few days of the interview. The survey received ethics approval from the Center for Disease Control of Iran, and all participants gave verbal informed consent.

2.2. PA assessment

The second version of the Global Physical Activity Questionnaire (GPAQ) was used in the survey [17]. This questionnaire, which has been developed by the World Health Organization, is composed of 16 questions about PA in a typical week and assesses PA in 3 domains: work, transportation, and recreational activities. The evaluation of PA in these domains is one of the factors that make GPAQ distinct from other questionnaires such as the less sophisticated, short version of the International Physical Activity Questionnaire (available at: http://www.ipaq.ki.se). It also determines the intensity of activity (ie, vigorous or moderate) in each domain as well as the time spent on sedentary behaviors such as watching TV. *Sedentary behavior* was defined as activities such as sitting at a desk, traveling in car/bus/train, reading, working with computer, and watching television.

To measure energy expenditure, the concept of metabolic equivalent (MET) was used. Metabolic equivalent is the ratio of a person's working metabolic rate relative to the resting metabolic rate [17]. *One MET* is defined as the energy cost of sitting quietly and is equivalent to a caloric consumption of 1 kcal/(kg h). It is estimated that a person's caloric consumption is 4 times as high when moderately active and 8 times as high when vigorously active. Therefore, to calculate a person's overall energy expenditure, 4 METs are assigned to the time spent on moderate activities and 8 METs to the time spent on vigorous activities. The total physical activity (TPA) score was calculated as the sum of all METs × minutes for moderate- or vigorous-intensity PA performed in work, commuting, and recreation. It should be noted that the GPAQ term *MET* is a rough alternative to what exercise physiologists define as MET, that is, 1 MET being 3.5 mL/min of oxygen consumption per kilogram of body weight [18].

Based on the GPAQ analysis framework [17], our participants were classified into the following 3 categories:

1. High PA: A person reaching any of the following criteria is classified in this category:
   - Vigorous-intensity activity on at least 3 days a week achieving a minimum of at least 1500 MET-minutes per week or
   - Seven or more days (per week) of any combination of walking and moderate- or vigorous-intensity activities achieving a minimum of at least 3000 MET-minutes per week.

As an example, moderate-intensity activity 5 days per week and vigorous-intensity activity 4 days per week sums up to 9 days per week of a combination of moderate- or vigorous-intensity activity, placing the person in the high-activity category.

2. Moderate PA: A person not meeting the criteria for the "high" category, but meeting any of the following criteria is classified in this category:
   - Three or more days (per week) of vigorous-intensity activity of at least 20 minutes per day or
   - Five or more days (per week) of moderate-intensity activity or walking of at least 30 minutes per day or
   - Five or more days (per week) of any combination of walking and moderate- or vigorous-intensity activities achieving a minimum of at least 600 MET-minutes per week.
3. Low PA: A person not meeting any of the above-mentioned criteria falls in this category.

2.3. Physical examination and biochemical measurements

Weight and height were measured in light clothing and without shoes. Portable calibrated electronic weighing scale and portable measuring inflexible bars were used for this purpose. Waist circumference (WC) was measured using constant tension tape at the end of a normal expiration, with arms relaxed at the sides, at the midpoint between the lower part of the lowest rib and the highest point of the hip on the midaxillary line. The body mass index (BMI, in

kilograms per square meter) was calculated according to the Quetelet formula.

Five milliliters of venous blood was taken in sitting position, centrifuged, and transferred under cold chain condition to the laboratory. Serum leptin concentrations were measured in the endocrine laboratory of Vali-Asr hospital (Tehran University of Medical sciences, Tehran, Iran) with an enzyme-linked immunosorbent assay (DRG Instruments, Marburg, Germany) with an intraassay coefficient of variation of 5.9% to 6.9% and an interassay coefficient of variation of 8.6% to 11.5%.

2.4. Statistical analysis

Complex sample survey analysis was performed using SPSS 17 for Windows (Chicago, IL). Data were weighted for sex, age, and residential area (urban/rural) strata, according to the population of Iran (national census, 2006). Data are expressed as mean ± standard error of mean. Partial correlation coefficients were calculated between leptin and features of PA after adjustment for various variables. Adjusted values of leptin were compared between PA categories using the general linear modeling method. $P < .05$ was considered statistically significant.

3. Results

After excluding participants with missing data (n = 213), analyses were performed in the remaining 3001 individuals. Anthropometric characteristics of participants are presented in Table 1. Leptin was significantly associated with age ($r = 0.061$, $P = .045$ in men and $r = 0.075$, $P = .011$ in women), BMI ($r = 0.414$, $P < .001$ in men and $r = 0.490$, $P < .001$ in women), and WC ($r = 0.359$, $P < .001$ in men and $r = 0.411$, $P < .001$ in women). Leptin was significantly higher in urban residents vs rural residents in both men (4.17 ± 0.10 vs 3.64 ± 0.12, $P = .001$) and women (11.60 ± 0.25 vs 9.70 ± 7.04, $P < .001$). After adjustment for BMI and WC, this association disappeared. In men, leptin was significantly lower in current smokers vs ex-smokers or never smokers (3.75 ± 0.14 vs 4.10 ± 0.09, $P = .035$). In women, current smokers had higher serum leptin levels vs ex-smokers or never smokers (13.02 ± 1.63 vs 10.90 ± 0.20, $P = .116$). After adjustment for BMI or WC, these associations disappeared. Total PA was inversely associated with age ($r = -0.212$, $P = .002$ in men and $r = -0.173$, $P = .005$ in women), BMI ($r = -0.338$, $P < .001$ in men and $r = -0.198$, $P = .001$ in women), and WC ($r = -0.357$, $P < .001$ in men and $r = -0.239$, $P < .001$ in women).

In both sexes, after adjustment for age, area of residence, BMI, WC, and smoking, leptin was significantly associated with TPA ($r = -0.129$, $P = .038$ in men and $r = -0.226$, $P = .006$ in women), duration of vigorous-intensity PA ($r = -0.120$, $P = .044$ in men and $r = -0.154$, $P = .019$ in women), duration of moderate-intensity PA ($r = -0.114$, $P =$

Table 1
Characteristics of study participants (SuRFNCD-2007, Iran)

	Men	Women	Total
n	1494	1507	3001
Age (y)[a]	39.42 ± 0.75	39.76 ± 0.78	39.59 ± 0.54
Area of residence			
Urban (%)	1011 (67.7)	1004 (66.6)	2015 (67.1)
Rural (%)	483 (32.3)	503 (33.4)	986 (32.9)
BMI (kg/m^2)[a]	25.4 ± 0.2	27.6 ± 0.2	26.5 ± 0.2
WC (cm)[a]	88.6 ± 0.4	88.8 ± 0.6	88.7 ± 0.4
PA category			
Low (%)	31.6 ± 1.1	48.6 ± 1.3	40.0 ± 1.0
Moderate (%)	22.3 ± 0.1	27.1 ± 1.2	24.7 ± 0.8
High (%)	46.1 ± 1.3	24.3 ± 1.2	35.4 ± 1.1
Smoking status			
Never smoker (% ± SE)	65.0 ± 1.8	97.5 ± 0.3	81.0 ± 1.3
Ex-smoker (% ± SE)	8.9 ± 0.7	0.8 ± 0.2	4.9 ± 0.4
Current smoker (% ± SE)	26.1 ± 1.6	1.8 ± 0.3	14.1 ± 1.1
Leptin (ng/mL)[a]	4.0 ± 0.1	10.8 ± 0.3	7.4 ± 0.3

Variables (except age, sex, and area of residence) are standardized for age, sex, and residential area of the 2006 population of Iran.

[a] Mean ± SE.

Table 2
Association between several features of PA and serum leptin after adjustment for potential confounders (SuRFNCD-2007, Iran)

	Men		Women	
	r	*P*	*r*	*P*
TPA				
Adjustment for:				
Age and area of residence	−0.217	.007	−0.214	.008
Age, area of residence, BMI, WC, and smoking	−0.129	.038	−0.226	.006
Age, area of residence, BMI, WC, smoking, and duration of sedentary behaviors	−0.098	.048	−0.189	.013
Duration of vigorous activity				
Adjustment for:				
Age and area of residence	−0.178	.019	−0.142	.023
Age, area of residence, BMI, WC, and smoking	−0.120	.044	−0.154	.019
Age, area of residence, BMI, WC, smoking, duration of moderate activity, and sedentary behaviors	−0.077	.064	−0.127	.029
Duration of moderate activity				
Adjustment for:				
Age and area of residence	−0.145	.029	−0.158	.020
Age area of residence, BMI, WC, and smoking	−0.114	.047	−0.160	.018
Age, area of residence, BMI, WC, smoking, duration of vigorous activity, and sedentary behaviors	−0.084	.059	−0.129	.033
Duration of sedentary behaviors				
Adjustment for:				
Age and area of residence	0.268	.001	0.283	<.001
Age, area of residence, BMI, WC, and smoking	0.194	.014	0.204	.007
Age, area of residence, BMI, WC, smoking, and TPA	0.172	.018	0.184	.014

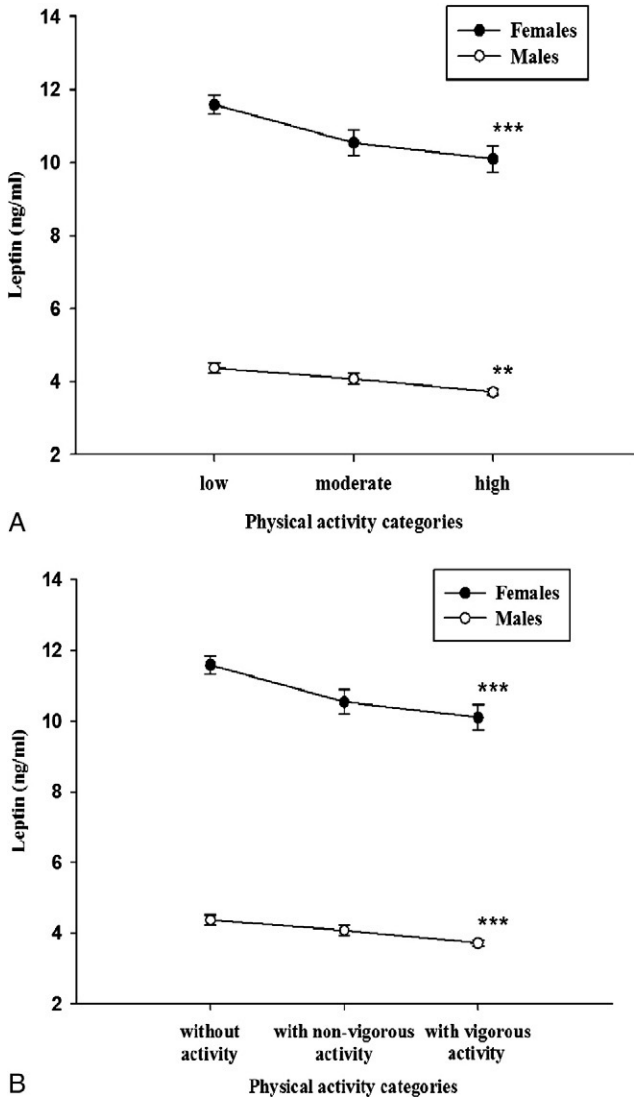

Fig. 1. After adjustment for age, residential area, BMI, WC and smoking there was a significant association between leptin and physical activity categories (low, moderate and high [A], without activity, with non-vigorous activity and with vigorous activity [B]) in males and females. (SuRFNCD-2007, Iran) $^{**}P < .01$, $^{***}P < .001$.

.047 in men and $r = -0.160$, $P = .018$ in women), and sedentary behaviors ($r = 0.194$, $P = .014$ in men and $r = 0.204$, $P = .007$ in women). The association between leptin and TPA was independent of the duration of sedentary behaviors ($r = -0.098$, $P = .048$ in men and $r = -0.189$, $P = .013$ in women; Table 2). In both sexes, after adjustment for age, residential area, BMI, WC, and smoking, there was a significant inverse association between leptin and higher PA categories (Fig. 1).

4. Discussion

Regulation of weight is a complex process that is controlled by a complex network of neural signals that drive the propensity for the intake and expenditure of energy. Many of the hormones involved in this feedback process act centrally to control hunger and satiation, as well as fatigue and energy expenditure. Thus, these hormones (including leptin) control both sides of the energy balance equation. The role of leptin in energy balance is unknown. Rodents lacking endogenous leptin are characteristically hyperphagic, physically inactive, obese, and insulin resistant [19,20]; yet administration of exogenous leptin stimulates PA in these animals [11,21]. Similar effects have been observed in humans. Within the general population, however, leptin secretory defects are rare; and resistance to leptin may be common, particularly in obese individuals [22]. Leptin secretion is regulated by hormones, including glucocorticoids, catecholamines, and insulin [23,24]. The increase in serum concentration of amino acids and insulin after a meal leads to an increase in leptin biosynthesis [24]. Fasting results in a gradual decline in serum leptin that is probably attributable to the decline in insulin and the ability of catecholamines to decrease leptin expression. The increased leptin expression observed in obesity could result from the chronic hyperinsulinemia and increased cortisol turnover over the long term [25]. Leptin response to PA is not well established and may depend on duration and intensity of activity [26]. In the present study, we investigated the relationship between fasting serum leptin concentrations and PA in a sample of Iranian adult population. In line with population-based, cross-sectional, epidemiologic studies [3] and studies in people with anorexia nervosa [4], leptin levels were negatively related to PA (independent of obesity), suggesting that leptin plays a role in energy expenditure in humans.

We are aware of only a few studies on the relationship between PAEE and leptin levels within free-living populations. Two of these were ecological comparisons of rural and urban populations in distinct ethnic groups [27,28], and 2 used invalidated questionnaires to assess PAEE [29,30]. In another study with a subjective assessment of PAEE, the Paffenbarger questionnaire was used [31]. From the ecological studies, one found a positive association of leptin with urban residence [28], whereas the other found a positive association with rural residence [27]. From the studies that used questionnaires, one found no association [30], whereas the other 2 studies reported an inverse association between leptin and PAEE [29,31]. Another study used objective measurement through doubly labeled water, but was small in size (n = 46) and focused on older sedentary African Americans [9]. The results of a free-living population-based cohort study (n = 758) by Franks et al [3] indicated that leptin was significantly associated with resting energy expenditure, but not with total or PAEE in women. No indices of energy expenditure were associated with leptin in men. It has been suggested that correcting the measures of energy expenditure for fat mass may negate the relationship between leptin and energy expenditure because of the extremely good correlation between leptin and fat mass [10]. Furthermore, it has

been argued that fat mass may be an inappropriate covariate, as it is relatively inactive and accounts for only 4% of whole-body oxygen consumption [10]. Failure to adjust energy expenditure for fat mass may lead to a confounding effect by not removing the effect of fat mass on energy expenditure.

However, our findings are in contrast to those from studies in the *ob/ob* mouse [5,11], Pima Indian children [13], and postmenopausal African Americans [9,10], which suggest that serum leptin is positively associated with energy expenditure and PA, and another study that, after controlling for adiposity, reports no relationship [7]. In murine experiments, exogenous leptin administration to animals deficient in leptin increased PA [11]. In healthy humans, on the other hand, leptin reduces PA. Some exercise intervention trials show that leptin level declines after exercise [32], whereas others show no effect [33,34]. Importantly, none have shown that exercise increases leptin levels. Most studies involving exercise interventions have not adequately addressed the nature of this relationship, partly because individuals who adhere to exercise interventions may have declined levels of other forms of energy expenditure [35]. Moreover, pre- and postintervention differences in leptin levels may be due to factors unrelated to fitness or activity, which were not satisfactorily dealt with by post hoc adjustment in the majority of the available reports.

Several mechanisms have been proposed for the inverse association between PA and serum leptin concentrations [36,37]. One pathway through which leptin may influence PA is via activation of the melanocortin-4 receptor in the arcuate nucleus [38,39]. High baseline leptin levels may reflect central leptin resistance in the arcuate nucleus, which in turn leads to reduced PA. Some investigators have noted that activation of the sympathetic nervous system by leptin results in increased concentrations of catecholamines [40-42], which may attenuate leptin synthesis and release [43]. This observation is supported by reports from Couillard et al [44] demonstrating that plasma leptin is reduced after an epinephrine infusion in both lean and obese women. Alternatively, PA may influence serum leptin concentrations directly through its impact on leptin synthesis [45,46]. Leptin messenger RNA expression is reduced in genetically obese rats after exercise training [45], and moderate-intensity PA results in a reduction of abdominal fat leptin synthesis in humans [46]. Improved insulin sensitivity secondary to PA may affect leptin synthesis and concentrations, independent of the adipose tissue mass [37]. We have previously reported the cross-sectional relationship between leptin, metabolic syndrome, and insulin resistance [47]. Given that PA is a strong determinant of insulin sensitivity, both with and without changes in adiposity [6], and leptin appears important in controlling insulin sensitivity and promoting PA, PA may mediate the relationship between leptin and insulin resistance. These observations are consistent with reports in rodents [48] and suggest that, in humans, leptin signaling may involve molecular targets that control the propensity for energy expenditure and the capacity for insulin signaling. Regardless of the mechanism, results from both animal and human studies using diverse methodologies suggest that PA is an independent determinant of leptin concentrations in the peripheral circulation.

A number of limitations in our study merit discussion and consideration. First, the cross-sectional nature of this study precludes the determination of causality. Second, a single measurement of plasma leptin is likely to have clouded the true relationship between PA and plasma leptin concentrations. Diurnal variation in leptin concentration may have also influenced our results. Third, measurement error from the use of self-reported PA is likely to have occurred. Fourth, accurate methods to estimate body adiposity, such as hydrodensitometry, were not feasible in the present study. Adjustment for body adiposity was, therefore, imperfect; and residual confounding cannot be excluded. This study is the first epidemiologic study with specific focus on the association between serum leptin and PA using a valid international PA questionnaire, which provides the possibility for comparison of our results with other populations. We investigated the association between leptin and different intensities (vigorous and moderate) and domains of PA in a large nationally representative sample. In addition, we evaluated the association between serum leptin and the duration of sedentary behaviors. This has not been sufficiently studied in previous work. Furthermore, we used adjusted models to control for important confounding factors (such as obesity) when evaluating the independent association between leptin and different features of PA. Our findings suggest that PA, a modifiable trait, is correlated with serum leptin levels. Prospective studies to consider objective measures of PA and adipose tissue mass are needed to elaborate on our findings.

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