The relationship between circulating levels of IL-18 and leptin, HsCRP, blood pressure and cardiorespiratory function in obese and lean men

Fatah Moradi [1]

Deprtment of Physical Education and Sport Sciences [1], Saghez Branch, Islamic Azad University, Saghez, Iran.

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Original Article

Abstract

Introduction: Interleukin-18 (IL-18) is a proinflammatory cytokine that is produced in adipose tissue and skeletal muscle. The circulating levels of IL-18 increases in obesity and some metabolic and cardiorespiratory diseases. The aim of the present study is to investigate the relationship between circulating levels of IL-18 and leptin, high-sensitivity C-reactive protein (HsCRP), blood pressure and cardiovascular function in obese and lean men.

Methods: In a descriptive-analytical study, 19 obese men (Body Mass Index (BMI) ≥ 30 kg/m^2) and 19 lean men (BMI ≤ 18) were selected as subjects. After 12 hours of fasting, blood samples were collected and general characteristics of the subjects were measured. The Pearson's correlation coefficient at a significance level of $P<0.01$ was used to analyze the collected data.

Results: Serum IL-18 levels in obese men were directly correlated with BMI and body fat percentage (BFP), but no significant correlation was observed in lean men. IL-18 in obese and lean men was directly correlated with leptin and HsCRP. But, it was inversely correlated with cardiorespiratory function (VO_2max). IL-18 levels in obese men were directly correlated with systolic blood pressure (SBP), but no significant correlation was found between IL-18 levels and diastolic blood pressure (DBP). No significant correlation was observed between IL-18 levels and SBP and DBP in lean men.

Conclusion: It seems that changes in anthropometric characteristics, blood pressure, cardiorespiratory function and hormones such as leptin and HsCRP can be effective in IL-18 changes. These findings reveal the role of IL-18 in some inflammatory, metabolic (including diabetes and metabolic syndrome) and cardiovascular (hypertension pressure and atherosclerosis) disorders, especially in obese patients.

Correspondence:
Fatah Moradi, PhD.
Physical Education and Sport Sciences, Saghez Branch, Islamic Azad University.
Saghez, Iran
Tel:+98 9144823733
Email:
moradi_fatah@yahoo.com

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Introduction:

Interleukin-18 (IL-18) is produced and released in adipose tissue and fat cells isolated outside the living organism body as well as the skeletal muscle (1). Like most well-known adipokines, IL-18 is primarily originated from non-adipose cells in the adipose tissue (1,2).

The relationships between circulating levels of IL-18 and different physiological variables may reveal the role of this cytokine in the inflammatory process and the pathogenesis of various metabolic and cardiovascular diseases (3,4). Leptin, as a peripheral hormone regulating long-term energy storage, reflects the amount of body fat (5). The relationship between the circulating levels of IL-18 and leptin is unclear. A study by Vilarrasa *et al.* (2006) indicates the lack of correlation between IL-18 and leptin (6).

C-reactive protein (CRP), as one of the most powerful predictors of cardiovascular diseases (7), can be produced in fat cells, but it is mainly produced by the liver in response to inflammation and also in response to factors released from fat cells such as tumor necrosis factor alpha (TNF-α).

CRP is significantly related with cardiovascular disease risk factors such as obesity, hypertension and dyslipidemia (8). There are not consistent findings on the relationship between CRP and IL-18 levels. Sun *et al.* (2011) studied the apparently healthy men and women and found a direct correlation between IL-18 levels and CRP (9).

However, Tsu *et al.* (2010) found no significant correlation between IL-18 and CRP levels in obese children (10).

There are also inconsistent findings on the relationship between blood pressure and IL-18 levels (6,9,11). Sun *et al.* (2011) found a direct correlation between the circulating levels of IL-18 and systolic blood pressure (SBP) and diastolic (DBP) in women, but they did not found a same correlation in men (9). In contrast, Jung *et al.* (2010) found an insignificant inverse correlation between IL-18 and SBP levels in overweight adolescents (11-13). However, higher concentrations of IL-18 have been found in patients with hypertension (6).

Some researchers have investigated the effects of exercise training on circulating levels of IL-18 (14,15). But there are little findings on the relationship between cardiorespiratory function and IL-18 levels. According to Stansold *et al.* (2012), exercise training reduced serum IL-18 levels in patients with metabolic syndrome (14). In contrast, Christiansen *et al.* (2010) found that.

Brown *et al.* (2007) found higher IL-18 plasma levels in obese than in lean people (1). In addition, a direct correlation was observed between plasma levels of IL-18 and body mass index (BMI) and body fat percentage (BFP) (9). On the contrary, Vilarrasa *et al.* (2006) conducted a study on healthy men and women and found no significant difference between IL-18 levels in obese and normal-weight healthy men and women. In addition, IL-18 levels were not correlated with anthropometric characteristics and body composition (16-19). Ada *et al.* (2013) found no significant correlation between IL-18 concentration and weight, BMI or BFP in men with normal weight (16,20,21).

Due to the limited findings, especially in the case of lean people, this study aimed to investigate the relationship between circulating levels of IL-18 and leptin, HsCRP, blood pressure and cardiorespiratory function in obese and lean men.

Methods:

This is a descriptive-analytical study. The target population were 20 to 30-year-old university youth with a BMI higher than 30 (obese volunteers) or those with a BMI less than 18.5 (lean volunteers). Meanwhile, based on the health history questionnaire, those that were habitually inactive (no physical activity in the 6 months before the study) in terms of previous exercise were admitted. After obtaining a written consent from volunteers, they were medically examined to verify their health. Volunteers with a history of cardiovascular disease, diabetes, thyroid diseases and any pathological condition or those taking any medication (with or without prescription) or those under any type of diet or other treatments were excluded from the study. Any drug addiction, smoking, alcohol and caffeine consumption led to exclusion from the study. Eventually, of the remaining obese volunteers (n=28), 20 obese people were randomly selected. Among the remaining lean volunteers (n=25), 20 patients were randomly selected for the lean group. Of course, one of the subjects in the obese group and a lean subject did not complete the measurements. Thus, the final sample consisted of 38 patients (19 obese and 19 lean men).

The research protocol was implemented over a period of almost a week.

First Day: During a briefing meeting in the laboratory, the objectives, research plan and

methodology, the test protocol to assess VO2max (cardiorespiratory performance indicator) and laboratory assessments and timing of the investigation were described for the volunteers in detail. In addition, participants were asked to attend for testing and sampling in fasting at 8 am (22).

Fifth Day: After three days of rest (to ensure compliance with the recommended tips), the subjects were asked to attend in the fitness club at 8 am. On this day, the general characteristics of the subjects (age, height, weight, BMI, body fat percentage, resting blood pressure) were recorded.

Sixth Day: Blood samples were taken from the basilica vein of resting subjects at 8 am. 5 ml of serum was taken at rest to determine the serum levels of IL-18, leptin and HsCRP. Serum samples were kept at -20°C until measurements.

Seventh Day: On this day, the cardiorespiratory function of the subjects was measured by VO_2max assessment at 8 am.

The fitness club and laboratory were equipped with a ventilation system. The ambient air was cool and dry (humidity of about 50%) and the temperature ranged from 22 to 25 ° C during the exercise.

Data collection tools

The subjects were weighed using a calibrated digital balance with a minimum accuracy of 0.1 (WS 80, Switzerland). The height was measured using a stadiometer equipped with a Broca plate with a minimum accuracy of 0.1cm (Machinen AG, Switzerland). BMI was calculated by dividing the body weight (kg) by the square of height (m^2). By measuring the subcutaneous fat at three points of the body (chest, triceps and subscapular region) by a caliper (with a minimum accuracy of 1 mm, Harpenden, English), the body density was calculated by Jackson and Pollock formula (23):

Body density = $1.1125025 - 0.0013125 (X_1) + 0.0000055 (X_1)^2 - 0.0002440 (X_2)$

X_1 = Total fat in the chest, triceps and subscapular region

X_2 = age

The body fat percentage was calculated using the Siri formula (24).

Body fat percentage (BFP) = (495/body density) – 450

Resting blood pressure in a sitting position was measured by a mercury sphygmomanometer after 10 minutes of rest. Measurements were performed twice and their average was calculated and recorded (23-25).

The Astrand-Rhyming submaximal test was conducted on a cycle ergometer (magnetic fixed cycle, ROBIMAX 7750, Taiwan) to determine VO_2max. The Astrand-Rhyming submaximal test is in fact the modified version of Young Men's Christian Association (YMCA) protocol developed by Siconolfi (Siconolfi cycle ergometer test).

During the implementation of this protocol for men, the test begins with an initial working pressure of 50 W and the working pressure increases 50 W every two minutes. The test continues until the heart rate of subjects reach more than 70% of the maximal heart rate (age-220). The heart rate was monitored using a digital wrist sphygmomanometer (Fresh Life, MS-906, Mars Medical, Taiwan). After reaching 70% of the maximum heart rate, pedaling continues less than two minutes to reach a stable constant heart rate. Then, using the work done by subjects (in watts) and the constant heart rate in the Astrand-Rhyming nomogram, the maximum oxygen intake is determined to estimate the maximum oxygen consumption using the following equation (26):

Oxygen consumption (l/min) = $0.348 (X_1) - 0.035 (X_2) + 3.011$

X_1: the maximum oxygen consumption estimated from the Astrand-Rhyming nomogram (liters per minute)

X_2: age (years)

The isocaloric diet consisted of 15% protein, 55% carbohydrates and 30% fat. The diet was administrated according to the basal metabolic rate (BMR) and activity of participants. For this purpose, the standard Harris- Benedict formula with an activity factor of 1.2 based on the age, gender and activity of subjects was used to estimate the total daily energy expenditure (21).

Basal metabolism rate (kcal) = $66 + (13.7 \times$ weight (kg)) + ($5 \times$height (cm)) - ($16.8 \times$ age (year))

Total daily energy expenditure (kcal) = basal metabolism rate (kcal) × (1.55 or 1.2)

The serum IL-18 and leptin levels were measured by ELISA method (Awernes Stat Fax 303 Plus, US) respectively with Human IL-18 Platinum ELISA Kit (intra-assay CV of 6.5%, inter-assay CV of 8.1%, a sensitivity of 9 pg/ml, eBioscience, US) and Leptin Human ELISA KIT (intra-assay CV of 5.7%, inter-assay CV of 8.6%, a minimum detection limit of 0.17 ng/ml, BioVendor, Germany). The serum HsCRP level was measured by quantitative **chemiluminescence** (Berthold, Germany) using (High Sensitivity CRP (hs-CRP) kit (intra-assay CV of 5.3%, inter-assay CV of 7.9%, sensitivity of 0.2 µg/ml, Monobind Inc., US).

The Kolmogorov-Smirnov test was used to examine the normal distribution of the population. Descriptive statistics (mean±SD) was used to describe data. The independent t-test was used for the comparison of means. The Pearson's correlation coefficient was used to evaluate correlations. A significance level of $\alpha \leq 0.01$ was considered in all tests. Statistical analysis was performed with the help of SPSS 22.

Results:

Table 1 shows the general characteristics of the subjects. The Pearson's correlation coefficient between the serum IL-18 level and selected variables is reported in Table 2.

Table 1. The general characersiticis of teh subjects

Parameter	Subjects	
	Obese	Lean
Age (years)	27.5±5.8	26.9±5.6*
Height (m)	176±5.05	179±6.12
Weight (kg)	93.5±8.95†	64.2 ±7.54
Body fat percentage (%)	32.8±3.5†	19.5±2.8
BMI (kg/m²)	31.03±3.59†	18.47±2.17
SBP (mmHg)	129±3	122±2
DBP (mmHg)	81±1	82±2
VO2max (ml/kg.min)	26.2±6.5†	32.1±5.3
IL-18 (pg/ml)	345.2±53.7†	202.4±45.3
Leptin (ng/ml)	8.0±3.8†	1.6±0.9
HsCRP (µg/ml)	4.0±3.7†	0.5±0.3

* Numbers are expressed as mean±SD, † indicates a significance level of $P<0.01$

According to the Pearson's correlation test results, serum IL-18 level in obese men is directly correlated with BMI ($P=0.006$) and BFP ($P=0.002$). However, no significant correlation was observed in the lean group ($P=0.078$ and 0.092, respectively). The serum IL-18 levels in both obese and lean men are directly correlated with leptin ($P=0.000$ and 0.003, respectively) and HsCRP ($P=0.008$ and 0.003, respectively). The serum IL-18 concentrations in obese men were directly correlated with SBP ($P=0.004$), but no significant correlation was found between the serum IL-18 levels and DBP ($P=0.067$). No significant correlation was observed between the IL-18 levels and SBP ($P=0.141$) and DBP ($P=0.218$) in lean men. The serum IL-18 levels in both obese and lean men were inversely correlated with VO_2max ($P=0.006$ and 0.009, respectively).

Table 2. The r values (teh Pearson's correlation coefficient) between serum IL-18 levels and selected variables

Parameter	Subjects	
	Obese	Lean
Body fat percentage (%)	+0.31*	+0.10
BMI (kg/m²)	+0.37*	+0.12
SBP (mmHg)	+0.21*	+0.05
DBP (mmHg)	+0.19	+0.1
VO2max (ml/kg.min)	-0.24*	-0.13*
IL-18 (pg/ml)	+0.13*	+0.09*
Leptin (ng/ml)	+0.21*	+0.14*

* a significant correlation at a level of $P<0.01$

Conclusion:

According to the results, the serum IL-18 level is higher in obese men than in lean men. These findings are consistent with the findings of many previous studies (2,9,27). Brown *et al.* (2007) studied obese and lean men and women and found higher IL-18 levels in obese people than in lean people (2). Sun *et al.* (2011) also found that obese/overweight people have a higher IL-18 level compared with normal-weight people (9). In contrast, Vilarrasa *et al.* (2006) found no difference in IL-18 levels in obese and normal-weight people (6). These discrepancies can be attributed to different subjects under study in terms of gender, age and BMI (2,6,9,27). However, the higher IL-18 levels in obese can be related to two factors.

First, according to Brown *et al.* (2007), the expression of IL-18 mRNA in adipose tissue of obese people is higher than in lean people. Although they believe that changes in IL-18 levels are due to changes in the insulin resistance rather than obesity, since insulin resistance in obese people is higher than in lean people, higher IL-18 level in obese people is predictable from this point of view (2). Furthermore, obesity is a known as a situation with low-grade inflammation, whereas the production of IL-18 is increased in inflammatory situations (1-3).

Based on the findings of the present study, serum IL-18 level is directly correlated with BMI and BFP in obese men. However, a similar correlation was not observed in lean men. This finding is consistent with the findings of some other studies (2,6,9,16,28). Accordingly, given that the ratio of lean mass and fat mass is different in obese and lean men, the relationship between the IL-18 levels and BMI and BFP is also different in obese and lean men. It seems that these inconsistent findings are due to different methods used to assess body composition (29).

According to the results, the serum IL-18 level in obese patients is directly correlated with SBP, but no correlation was found between the serum IL-18 levels and DBP. In addition, no correlation was found between IL-18 levels and blood pressure in lean men. According to literature, high levels of blood pressure are associated with high circulating levels of IL-18 (30) so that IL-18 level is higher in patients with hypertension (6). In line with the findings of this study, Evans *et al.* found a direct correlation between mean SBP and IL-18l levels in normal weight and obese women (28). Nagy *et al.* found a direct correlation between IL-18 levels and SBP (31). They also found a significant correlation between the serum IL-18 levels and SBP ($P=0.075$) and DBP ($P=0.054$) in Japanese men [16]. However, Jung *et al.* found no significant correlation between IL-18 levels and SBP in overweight adolescents (11).

The findings of this study showed a direct correlation between the circulating levels of IL-18 and leptin in both obese and lean men. There are very little findings on the relationship between the circulating levels of IL-18 and leptin. Given the major role of fat mass in circulating levels of leptin (5) and IL-18 (32), their direct correlation can be interpreted through the role of the adipose tissue in the secretion of these hormones (33).

The results showed a direct correlation between the circulating levels of IL-18 and HsCRP in obese and lean men. Literature indicates the correlation between plasma circulating levels of IL-18 and several inflammatory markers (9-11,34,35). Since CRP levels indicate an inflammatory situation, the correlation between IL-18 levels and HsCRP could indicate the mediating role of IL-18 in inflammation (11).

The findings also showed an inverse correlation between serum IL-18 levels and cardiorespiratory function index (VO_2max) in obese and lean men. These results are consistent with the findings of several studies in this area (16,26,27). The inverse correlation between IL-18 levels and VO2max can be justified in this way that people with a higher level of physical fitness (with a higher VO_2max) have a lower body fat percentage (BFP) or lower expression of IL-18 leading to a lower circulating level of IL-18 (27,36).

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