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ORIGINAL ARTICLE

Effects of Resistance versus Endurance Training on Plasma Lipocalin-2 in Young Men

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Abstract

Purpose: **Lipocalin-2 (Lcn2) has been recognized as an adipocyte-derived acute phase protein that is positively correlated with obesity, insulin resistance, type 2 diabetes, and cardiovascular disease. The effects of resistance and endurance training (RT *vs.* ET) on plasma lipocalin-2 are still unclear. Therefore, the purpose of this study was to examine the effects of RT *vs.* ET on plasma lipocalin-2 in young men.**

Methods: **Twenty nine healthy and sedentary young men (age, 21-29 years) participated in this study. The subjects were randomly assigned to RT group (n=9), ET group (n=10) or control group (n=10). The experimental groups performed either RT or ET, 3 days a week for 8 weeks. The endurance training program included continuous running at an intensity corresponding to 65–80% of maximal heart rate, while resistance training consisted of 2-4 sets of circuit weight training for 8 stations and at an intensity corresponding to 65-80% of 1-RM in each station.**

Results: **No significant changes in the body mass, BMI, body fat percentage and WHR were found after the RT and ET. The results showed that Lcn2 decreased after RT and ET compared with the control group ($P<0.05$). High sensitivity C-reactive protein (hs-CRP) and insulin resistance determined by HOMA-IR, did not change in the RT and ET compared with the control group.**

Conclusion: **Lcn2 decreases after 8 weeks RT and ET, but this improvement was not accompanied by decreased hs-CRP and insulin resistance in healthy and sedentary young men.**

Key Words: Lipocalin-2 Protein, Human; Insulin Resistance; Resistance Training; Exercise

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INTRODUCTION

Obesity is the most common risk factor for insulin resistance, type 2 diabetes mellitus and cardiovascular disorders. Although the detailed molecular events that link obesity with its associated pathologies are not well understood, accumulating evidence suggests that systemic inflammation might be an important mediator [1,2]. Studies have demonstrated close associations between obesity and increased circulating concentrations of proinflammatory molecules, including acute-phase proteins, cytokines, adipokines, and chemokines [3,4]. In obese states, these proinflammatory factors are produced predominantly from enlarged adipocytes and activated macrophages in adipose tissue and liver. Many of these inflammatory factors, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and high sensitivity C-reactive protein (hs-CRP) can directly induce glucose intolerance and insulin resistance by antagonizing insulin's metabolic actions at peripheral tissues, especially in liver and skeletal muscle [5].

Lipocalin-2 (Lcn2), also known as 24p3 [6], is a member of the lipocalin protein family that was originally identified in mouse kidney cells and human neutrophil granules. This protein has been implicated in diversified functions such as apoptosis and innate immunity [7]. Lcn2 has been recognized as an

adipocyte-derived acute phase protein that is positively correlated with potential effects in obesity, inflammation and insulin resistance in mice and humans [7,8]. It also has been showing that circulating levels of this adipokine have a strong, direct correlation with hs-CRP as an acute phase protein [9]. One of the best strategies for preventing obesity and its associated inflammation is participation in regular physical activity [10]. On the other hand, exercise has been shown to have beneficial effects on obesity, type 2 diabetes and the metabolic syndrome. Although the changes in adipokine levels might be an important clue for understanding the beneficial effects of exercise, data on exercise-induced changes of Lcn2 is still unclear. Recently, Damirchi et al[11] reported that Lcn2 increased after a single bout of graded exercise in obese and normal-weight men. Choi et al[8], in an only available study, did not report that any changes in Lcn2 level in obese women after 12 weeks moderate exercise training. The magnitude of the changes in plasma adipokine levels depends on the type, duration and intensity of exercise [10]. The physiological and biochemical responses to resistance exercise are different from those exhibited in response to endurance exercise [12]. No previous study has investigated the effects of resistance exercise on Lcn2 concentration, and no previous studies have attempted to compare the responses of Lcn2 to both resistance and endurance exercise in young men. We hypothesized that resistance training (RT) and endurance training (ET) would reduce the adipose tissue, insulin resistance, inflammatory markers and Lcn2 concentrations. Therefore, the present study was designed to determine and compare the effects of RT and ET on body composition, insulin resistance, CRP and Lcn2 concentration in healthy and sedentary young men.

METHODS AND SUBJECTS

Subjects:

Thirty healthy and sedentary young men (25.3±2.3 years; mean ± SD) participated in this study. All the subjects were asked to complete a personal health and medical history questionnaire, which served as a screening tool. The subjects were given both verbal and written instructions outlining the experimental procedure, and written informed consent was obtained. Our participants were not engaged in any systematic exercise programs at least 6 months before the study, they were nonsmokers and none of them had any disease. All the subjects completed the 3-day diet recall forms and were instructed to maintain their normal physical activity and dietary habits throughout the study. The subjects were randomly assigned to one of the RT group (n=10), ET group (n=10) or control group (n=10). The study was approved by the Islamic Azad University, Gachsaran branch Ethics Committee.

Study design:

Following familiarization, subjects were asked to report to the laboratory for an additional test session designed to determine one-repetition maximum (1-RM) for 8 exercises involving the upper and lower body. Maximal strength was determined using a concentric, 1-RM [13], as previously described [14]. The warm-up consisted of riding a stationary bicycle for 5 min, two sets of progressive resistance exercises similar to the actual exercises utilized in the main experiment, and 2-3 min of rest accompanied by some light stretching exercises. After the warm-up, subjects performed the 1-RM test, and the heaviest weight that could be lifted once using the correct technique was considered as 1-RM for all the exercises and used to calculate the percentage of resistance.

Resistance training: Two familiarization sessions were designed to habituate subjects with the testing procedures and laboratory environment. The main aim of these sessions was to familiarize subjects with different resistance exercises using weight-training machines and also to familiarize them with performing the 1-RM test. During the familiarization sessions, it was ensured that all the subjects used the correct techniques for all exercises prior to taking part in the main test sessions. Subjects executed eight resistance exercises selected to stress the major muscle groups in the following order: chest press, leg extension, shoulder press, leg curls, latissimus pull down, leg press, arm curls, and triceps extension. RT consisted of

50-60 min of circuit weight training per day, 3 days a week, for 8 weeks. This training was circularly performed in 8 stations and included 2-4 sets with 8-12 maximal repetitions at 65-80% of 1-RM in each station. Each circuit and set was separated by 2-3 min and 60-90 s rest respectively. General and specific warm-up were performed prior to each training session, as explained for the 1-RM determination, and each training session was followed by cool-down. One subject did not participate in the final examinations and was excluded.

Endurance training: The ET program consisted of running at 65–80% of maximal heart rate (HR_{max}) for 20–34 min per day, 3 days per week, for 8 weeks. The program started with 20 min running for the first few sessions, and this was then changed to 34 min per session until the end of training. Each training session was started with a warm-up and finished with a cool down. The exercise intensity was controlled by the investigators, using a heart rate monitor, who ensured that it was between 65 and 80% of HR_{max} throughout the trial.

Measurements:

Anthropometric and body composition measurements: Height and weight were measured, and body mass index (BMI) was calculated by dividing weight (kg) by height (m^2). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm) [15]. Body fat percentage was assessed by skinfold thickness protocol. Skinfold thickness was measured sequentially, in chest, abdomen, and thigh by the same investigator using a skinfold caliper (Harpenden, HSK-BI, British Indicators, West Sussex, UK) and a standard technique [15].

Measurement of maximal oxygen consumption: VO_{2max} was determined by Rockport One-Mile Fitness Walking Test. In this test, an individual walked 1 mile as fast as possible on a track surface. Total time was recorded and HR was obtained in the final minute [15]. VO_{2max} was calculated using the ACSM formula [15].

Energy intake and energy expenditure controls: All the subjects completed the 3-day diet recall forms and were instructed to maintain their normal physical activity and dietary habits throughout the study. The nutrient composition was determined by a computer nutritional analysis program (COMP-EAT 4.0 National Analysis System, London, UK) using the McCance and Widdowson Food Composition Tables.

Biochemical analyses: Approximately 10 milliliters of blood was collected into plain and EDTA filled vacutainer tubes after an overnight fast of at least 12 hours at the same time before and after 8 weeks intervention. The tubes were then centrifuged and serum and plasma was drawn off and stored at -80°C until analysis. The plasma Lcn2 level was measured in duplicate using enzyme-linked immunosorbent assay (ELISA) kits (Uscn Life Science Inc, Wuhan, China). The sensitivity of kit was 0.12 ng/ml. hs-CRP levels were determined in duplicate via ELISA kits (Diagnostics Biochem Inc., Canada). The intra and inter-assay coefficients of variation for hs-CRP were <5.7% and a sensitivity of 10 ng/ml. Plasma glucose was determined by the enzymatic (GOD-PAP, Glucose Oxidase-Amino Antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran). The intra and inter-assay coefficients of variation for glucose were<1.3% with a sensitivity of 1 mg/dl. The serum insulin level was measured by radioimmunoassay (RIA) and the insulin resistance index was calculated according to the homeostasis model assessment (HOMA-IR) which correlates well with the euglycemic hyperinsulinemic clamp in people with diabetes [16].

Statistical analysis:

Results were expressed as the mean±SD and distributions of all variables were assessed for normality. Main effects of training modality (resistance and endurance) and time (before and after 8 weeks) and interaction between training modality and time were assessed using two-way analysis of variance (ANOVA). When ANOVA indicated the presence of a significant difference, post hoc comparisons using Bonferroni's method were applied to identify which mean differences were statistically significant. The relationships between variables in the training groups were determined using Pearson's correlation test. The level of significance in all statistical analyses was set at

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Table 1: The composition of the subjects' diets (carbohydrate, fat and protein) and calorie intake during 8 weeks

	Control	Endurance training	Resistance training
Carbohydrate (g)	467.51(45.72)	499.44(47.81)	480.71(34.72)
Fat (g)	77.91(15.72)	79.97(12.17)	75.33(11.85)
Protein (g)	112.53(9.72)	114.22(9.43)	113.85(8.92)
Energy intake (kcal)	3121.14(29.72)	3173.52(22.17)	3059.55(20.16)

Data are the mean (SE) of carbohydrate, fat and protein consumption and calorie intake of subjects in each group. Results showed that the subjects maintained their dietary habits throughout the study.

P<0.05. Data analyses were performed using SPSS software for windows (version 13, SPSS, Inc., Chicago, IL).

RESULTS

Changes in diets composition and calorie intake:

All data were not significant for normality check. Data of carbohydrate, fat and protein consumption and calorie intake of subjects during eight weeks are given in Table 1. Results showed that the subjects maintained their dietary habits throughout the study.

Changes in anthropometric, body composition and physiological variables:

Anthropometric and body composition characteristics of the subjects at baseline and after training are presented in Table 2. Before the intervention, there were no significant differences in any of variables among the three groups. No significant changes in the body mass, BMI, body fat percentage and WHR were found after the RT and ET. After 8 weeks intervention, VO_{2max} increased (P<0.05) in the RT and ET groups, while no significant change in the control group was found.

Changes in muscular strength:

There were no differences in strength between control and RT groups at baseline (Table 3). Our results showed that muscle strength increased after 8 weeks RT (P<0.05).

Changes in biochemical variables:

Biochemical variables of the subjects before and after RT and ET are presented in Table 4. Our results showed that Lcn2 decreased after RT and ET compared with the control group (P<0.05). For hs-CRP, there was no significant difference between the RT, ET and the control groups. Fasting glucose, insulin and HOMA-IR did not change in the RT and ET compared with the control group (Table 4). Pearson's correlation demonstrated a significant positive relationship between plasma Lcn2 levels with body mass (r=0.37, P=0.03), body fat percentage (r=0.36, P=0.04) and WHR (r=0.5, P=0.004) at baseline. No significant relationship between plasma Lcn2 with biochemical and body composition variables were found in the RT and ET group after 8 weeks intervention.

Table 2: Physical and physiological characteristics of the subjects before and after training

Variable	Control		Endurance training		Resistance training	
	Pre	Post	Pre	Post	Pre	Post
Body mass (kg)	67.90 (9.04)	68.04 (9.10)	73.4 (15.1)	72.1 (10.4)	69.2 (15.7)	69.6 (9.9)
Body mass index (kg/m^2)	24.99 (3.36)	25.02 (3.3)	25.04 (3.1)	24.6 (2.9)	23.5 (3.2)	23.6 (2.7)
Body fat (%)	19.35 (5.09)	19.31 (5.16)	19.8 (4.3)	18.8 (4.5)	16.4 (4.7)	16.2 (4.8)
Waist hip ratio	0.84 (0.07)	0.84 (0.07)	0.86 (0.5)	0.86 (0.3)	0.86 (0.06)	0.86 (0.05)
VO_2max (ml.Kg^{-1}.min^{-1})	36.80 (3.96)	36.73 (4.13)	38.8 (3.03)	46.1 (2.8)[ab]	40.5 (2.3)	45.2 (3.3)[ab]

Data are the mean (Standard Error) of baseline and final values and of the anthropometric and body composition change on each variable in each group. Main effects of training modality (resistance and endurance) and time (before and after 8 weeks) and interaction between training modality and time were assessed using two-way analysis of variance (ANOVA).
[a] P<0.05, different from control group, [b] P<0.05, pretraining *vs.* post-training values

Table 3: Maximal strength (1RM) changes in the RT and control groups during the study

Variable	Control		Resistance training	
	Pre	Post	Pre	Post
Chest press	66.32(5.90)	66.41(6.13)	68.61(5.62)	83.11(6.85)[ab]
Shoulder press	54.50(6.13)	54.72(6.56)	57.96(2.20)	82.54(6.45)[ab]
Latissimus pull down	26.36(6.84)	26.31(6.10)	24.38(7.77)	37.16(9.95)[ab]
Arm curls	23.16(2.27)	22.99(2.38)	23.49(2.40)	30.10(2.47)[ab]
Triceps extension	22.8(7.73)	22.83(7.57)	24.46(1.53)	35.65(3.27)[ab]
Leg extension	49.09(9.84)	49.23(9.20)	47.63(1.71)	58.29(4.93)[ab]
Leg curls	26.54(6.70)	26.83(6.33)	25.67(5.58)	36.48(6.50)[ab]
Leg press	97.23(7.85)	97.09(7.53)	100.15(9.36)	118.87(09)[ab]

Data are the mean (standard error) of baseline and final values of the maximal strength (1RM) in each group
[a] $P<0.05$, different from control group, [b] $P<0.05$, pretraining *vs.* post-training values

DISCUSSION

Lcn2 has been identified as a novel adipokine associated with obesity, diabetes type 2 and the metabolic syndrome. The effects of resistance versus endurance training on plasma Lcn2 are still unclear, thus this study aimed to investigate and compare the effects of RT and ET on Lcn2 in young men. The present study demonstrated that plasma Lcn2 decreased after 8 weeks RT (10.3%) and ET (22.02%) compared with the control group (P<0.05), while no significant differences were found between two training groups. Although no previous study has investigated the effects of resistance exercise on Lcn2 concentration, Choi et al. [8] indicated that there was no significant change in the Lcn2 in obese women after 12 weeks moderate exercise training. This discrepant result may be attributed to variation in the exercise protocols and differences in subject populations. The results are in agreement with previous reports showing that there was a significant positive relationship between plasma Lcn2 levels with body mass, body fat percentage and WHR, suggesting that the increased fat mass might account for the elevated blood levels of this adipokine in obese individuals. Wang et al [7] showed a higher concentration of Lcn2 in obesity and this adipokine is positively related to the BMI, waist circumference and body fat percentage. Choi et al [17] demonstrated a positive relationship between Lcn2 and body mass and Damirchi et al [11] showed a positive relationship between Lcn2 level with waist circumference, fat mass and BMI. Although the results showed that plasma Lcn2 level had tendency to increase with the body mass, body fat percentage and WHR increased at baseline, no significant relationship between the change of plasma Lcn2 with body composition variables were found in the RT and ET group after 8 weeks intervention. Since there was no significant

Table 4: Metabolic characteristics of the subjects before and after training

Variable	Control		Endurance training		Resistance training	
	Pre	Post	Pre	Post	Pre	Post
Lipocalin-2 ($\mu g.l^{-1}$)	11.12(4.52)	13.05(2.04)	22.72(8.33)	17.71(6.89)[ab]	22.20(6.27)	19.91(6.50)[ab]
hs-CRP ($mg.l^{-1}$)	0.83(0.81)	0.89(0.80)	0.55(0.51)	0.78(0.70)	0.32(0.55)	0.32(0.55)
Fasting glucose ($mg.dl^{-1}$)	91.20(14.22)	87.12(12.10)	106.83(24.20)	81.11(10.82)[b]	100.63(14.15)	82.21(10.64)[b]
Fasting insulin ($\mu U.ml^{-1}$)	12.36(2.43)	10.96(3.01)	13.13(2.21)	9.82(2.73)[b]	15.6(2.78)	10.90(3.83)[b]
HOMA-IR	2.33(0.86)	2.73(0.63)	2.79(1.02)	2.42(0.40)[b]	3.81(0.82)	2.21(0.84)[b]

Data are the mean (standard error) of baseline and final values and of the anthropometric and body composition change on each variable in each group. Main effects of training modality (resistance and endurance) and time (before and after 8 weeks) and interaction between training modality and time were assessed using two-way analysis of variance (ANOVA). (hs-CRP: high sensitive C-reactive protein)
[a] $P<0.05$, differenct with control group, [b] $P<0.05$, pretraining *vs.* posttraining values

relationship between body composition parameters and plasma Lcn2, thus it seems that there should be the other parameters attributed in Lcn2 improvement.

Lcn2 can be recognized as an inflammatory marker that increases after a progressive physiological stress in sedentary individuals. Furthermore, increasing Lcn2 secretion from fat cells may be stimulated by lipopolysaccharides that suggest Lcn2 as an acute phase protein [7]. It is reported a direct relation between the Lcn2 and hs-CRP levels and Lcn2 can be use by researchers and clinicians as an inflammatory index [8]. Results showing no significant relationship between Lcn2 and hs-CRP after 8 weeks RT and ET, suggest that decrease of the other inflammatory markers might decrease Lcn2 concentration. Serum Lcn2 levels correlated with serum IL-6 and TNF-α levels in patients with psoriasis [18], while we did not measure IL-6 and TNF-α concentrations in this study. Additional research is needed to examine whether exercise–induced change in IL-6 and TNF-α concentrations decreases Lcn2.

On the other hand, Sommer et al [19] showed an upregulation of Lcn2 by IL-1 beta implicating a potential role of this adipocyte-secreted acute phase reactant in the development of insulin resistance, obesity and associated disorders, including cardiovascular disease. Sommer et al [19] and Yan et al [20] indicated a positive relationship between Lcn2 concentration and insulin resistance, however, we did not find a significant relationship between Lcn2 and insulin resistance determined by HOMA-IR. Choi et al [8] reported that HOMA-IR is not a very sophisticated measure of insulin resistance although it has been used widely in clinical and epidemiological studies.

Our results showed that 8 weeks RT and ET decreased Lcn2 concentration in young men and the effects of these exercises were similar. Therefore it seems that that exercise itself is effective in decreasing Lcn2 independent of exercise mode. Lcn2 can be recognized as an inflammatory marker and previous studies indicated that exercise has an anti-inflammatory nature [21]. In view of the anti-inflammatory nature of exercise, its beneficial action is seen not only in obesity, hypertension, coronary heart disease [22], insulin resistance [23], diabetes mellitus [23] and hyperlipidemias [22] but also in Alzheimer's disease and other conditions where inflammation plays a significant role [21]. We had some limitations in this study. We did not measure IL-6 and TNF-α in the present study. If we could measure these inflammatory markers, we could carefully explain the decrease of plasma Lcn2 in response to 8 weeks RT and ET in young men.

CONCLUSION

In summary, 8 weeks RT and ET decreased Lcn2 concentration in young men, while these exercises had no effect on body composition, hs-CRP and insulin resistance determined by HOMA-IR. In addition, there were no significant relationships between plasma Lcn2 with body composition, insulin resistance and hs-CRP after the intervention. Therefore, it is concluded that other mechanism such as exercise *per se* or decrease of the other inflammatory markers such as IL-6 and TNF-α might decrease Lcn2 concentration in young men. Additional research is needed to examine these mechanisms.

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Conflict of interests: None

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