



Effects of Aerobic Exercise on Serum Retinol Binding Protein4, Insulin Resistance and Blood Lipids in Obese Women

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Abstract

Background: Retinol binding protein4 (RBP4) is a type of adipokine which transports vitamin A to serum. RBP4 could be a bridge between obesity and insulin resistance. This study aimed to investigate the effects of aerobic exercises on RBP4 serum's concentration and metabolic syndrome risk factors in obese women.

Methods: Twenty obese women with body mass index $35.81 \pm 3.67 \text{ Kg/m}^2$, fat percentage 43.98 ± 4.02 , and waist to hip ratio 1.03 ± 0.05 were included and were randomly assigned to experimental and control groups. The experimental group received aerobic exercises for a period of 12 weeks each three sessions on treadmill workout. The treadmill speed were based on a 60-65 and 80-85 maximal heart rate percentage and duration of 15-20 and 45-50 minutes, at the beginning and the end of exercise, respectively. Body composition, serum glucose, insulin, TG, LDL-C, HDL-C, total cholesterol, and RBP4, were measured in both groups before and after the treatment by ELISA method. Insulin resistance was measured by HOMA-IR. To compare within group differences and between group comparisons t-correlated and t-independent tests were used, respectively.

Results: After 12 week aerobic exercises; weight, fat percentage, WHR, and BMI in the experimental group was significantly decreased ($P < 0.05$). RBP4, insulin, insulin resistance, TG and HDL-C had significant differences between two groups. The cholesterol level, LDL-C and glucose did not have any significant changes.

Conclusion: The aerobic exercises can decrease body composition, insulin resistance, TG, and RBP4, so it can be beneficial for obese women's health, because it.

Keywords: Aerobic exercises, RBP4, Metabolic Syndrome, Obese women, Insulin Resistance

Introduction

Obesity is known as a risk factor for the development of metabolic disorders such as chronic inflammation, insulin resistance, dyslipidemia, arterial hypertension and atherosclerosis (1). Most of obese individuals are in danger of metabolic syndrome (2). Adipokines are secreted proteins from adipose tissue. The production of some of the adipokines is resulted from obesity, type2 diabetics, and metabolic syndrome (3). Retinol binding protein 4 (RBP4) is a type of adipokine

related to the family of lipocalin proteins which transports vitamin A (retinol) to serum (4). RBP4 protein is synthesized mainly in the liver and adipose tissue (5). Adipose tissue may be a less important source for RBP4 concentrations in humans than animals (6). Although serum level of RBP4 in obesity, type2 diabetes, and metabolic syndrome is increased, the report is not accurate concentrations (7). Recently, higher RBP4 levels in obese and overweight individuals have been re-

ported (6). Besides, after adjustment for age, serum RBP4 had a positive relation with waist circumference, total abdominal fat and visceral fat. Visceral fat and LDL-C levels are independently influenced by RBP4 (8). RBP4 could be a bridge between obesity and insulin resistance (7). Cho et al (7) showed that human obesity is increased with RBP4 serum levels, and BMI is significantly higher than those of lean controls. In this study, there was not any relationship between plasma levels and the amount or percentage of body fat. Furthermore, the study by Broch et al (3) concluded that there was no relationship among insulin resistance, RBP4, and anthropometric measurements such as waist circumference, hip circumference, WHR, BMI, and fat mass. But RBP4 is related to blood pressure, triglycerides and LDL-C levels. RBP4 levels is related to systolic blood pressure, and obesity-related biochemical parameters (fasting glucose, fasting insulin, total cholesterol, LDL-C and insulin resistance index), even after adjustment for age and fat.

It is likely that increase in RBP4 level, will lead to increased in insulin resistance, dyslipidemia, and cardiovascular diseases (8).

Some studies in humans' RBP4 levels have shown inversely correlated insulin sensitivity and HDL-C levels. It is a point to mention that with some components of metabolic syndrome including BMI, triglyceride levels and systolic blood pressure there was a positive relationship (9, 8-13). Aerobic exercise will reduce the RBP4 levels in menopause women with type2 diabetes, middle-aged women, and young women (14, 15). A study showed that in response to four week exercise training in a wide age range of patients, RBP4 level was reduced (15). Moreover, Choy et al., after three months of exercise training did not observe significant differences in the levels of RBP4 in Korean women (16). As noted, obesity is one effective factor in increasing the levels of RBP4 in humans. Studies have also shown that the RBP4 level is much higher in obese people than in lean ones. Therefore, weight loss will reduce serum concentrations of RBP4 (3, 12). Studies have shown that a 5% weight loss, will lead to an increased insulin resistance index. Only slightly, the

RBP4 gene will reduces fat tissue. And RBP4 level is not affected by this amount of weight loss (6, 12). Other studies have described that improvement in metabolism after exercise can reduce RBP4 levels (6). This also improves insulin sensitivity caused by exercise training in humans which are associated with lower levels RBP4 (17). Another study showed that a decrease in body fat caused by exercise, leads to a decreased level of RBP4 (14).

According to the controversial studies on the exercise effect and RBP4 levels, few studies which have been done in this area, and because the exact mechanism of exercise effect on 4RBP reduction is not clear this study was designed.

Materials and Methods

This is a quasi-experimental research method. This study was confirmed in 2012 by Isfahan University of Medical Sciences our Institution Ethics Review Board for human studies and participants signed an informed consent. After initial screening, individuals with BMI more than 30kg/m² were selected. Athletes, smokers, patients, and persons who used a weight loss method were excluded from the study. No change in body weight over 2 kg and with no endocrine disorders, diabetes, cardiovascular diseases and chronic conditions had been invited, and then justified. Totally, 20 volunteers were selected. Then, participants were randomly assigned in to the experimental group (n=10) and controls (n=10) group. The average age of those women were 37.0±9.89 years.

All the variables, including age, height (the stadiometer brand was SECA, made in Germany, with a sensitivity of 1mm). weight, body fat percentage, body mass index, waist-hip ratio (In Body instrument , Model 3, and the brand name of BIOSPACE, made in Korea).

The serum glucose level (glucose monitoring kit, colorimetric enzymatic method, Pars Azmoon trading company, Tehran Iran, with a sensitivity of 1mg/dl). Serum insulin levels (ELISA Sandwich kit, Mercodia AB Company, Uppsala, Sweden,

with a sensitivity of 1mU/l). Insulin resistance (based on using homeostasis model, and by implicating Insulin and glucose concentrations were calculated). The level of HDL-C, LDL-C, TG, total cholesterol by the colorimetric kits from Pars Azmoon Trading Company made in Iran was measured. Serum RBP4 levels were measured using the ELISA Sandwich kit from Cusabio Co., China, was used.

The aerobic exercises consisted of warm-up exercises for 10 minutes (walking, stretching, and jogging) followed by principal aerobic activity. The task started by a maximum heart rate of 60-65%. In the first session, the duration for fast walking was 15-20 minutes. Progress during the first week was based on 60-75% of maximum heart rate and timing reached to 25-30 minutes. In the third week, the heart rate reached to 75-80%, and timing to 35-40 minutes. This process even lasted till the seventh week. In the seventh week, the heart rate was set to 80-85%, and timing to 45-50 minutes. This process lasted till the 12th week. At the end of each session, there was a slow cool-down time with stretching exercises which would last for 10 minutes.

Blood samples were collected in two stages; 24 hours before the start of the first session (pre-test), and 24 hours after the last session (after 12th week), after overnight fasting and at rest, at 8 am. Each time, 10ml blood sample was collected in the sitting position, and from the left anterior vein.

After 10 minutes samples incubation in room temperature, samples were centrifuged (10min, 3000rpm). The centrifugation was done to remove the serum from blood clots. Finally, the samples were frozen in -70°C.

Descriptive statistics was used to describe characteristics of the subjects, including age, height, weight, body mass index, body fat percentage, waist-to-hip ratio, serum glucose, and insulin, HDL-C, LDL-C, TG, TC and RBP4.

For Variables normality Kolmogorov-Smirnov test was used. To evaluate within groups differences t-dependent test, and to calculate differences between groups t-independent test were used. The significant level was set at $P<0.05$.

Results

Tables 1 and 2 show different variables between two groups. The amount of weight, BMI, WHR, and fat percentage was significantly reduced due to aerobic exercises ($P<0.05$).

The RBP4 level decreased significantly. Also, HDL-C, TG, insulin, and insulin resistance were also significant in comparison with control group ($P<0.05$). There was not any significant change in the serum glucose level. LDL-C level, and total cholesterol did not significantly decrease after a 12-week aerobic exercise ($P<0.05$).

Table 1: Individual characteristics of subjects in experimental and control groups

Statistical Indicators	Group	Pre-test Mean±SD	Post-test Mean±SD	Paired-T	Pvalue	Independent-T	P value
Weight(kg)	Control	86.8±6.21	86.32±5.73	1.475	0.17	3.61	*0.004
	experience	94.11±5.35	90.59±5.64	4.53	*0.001		
Fat percentage	Control	42.2±2.53	41.9±2.43	1.571	0.15	2.76	*0.013
	experience	44.87±4.39	43.29±4.53	3.53	*0.006		
BMI(kg/m ²)	Control	33.02±0.98	33.04±1.30	-0.16	0.87	3.40	*0.006
	experience	37.21±3.73	35.6±3.64	3.48	*0.007		
WHR	Control	1.01±0.03	1.00±0.02	0.93	0.37	2.39	*0.028
	experience	1.04±0.06	1.03±0.03	4.14	*0.002		

* Significance level $\alpha<0.05$

Table2: Change variables from pre-test to post-test in experimental and control groups

Statistical Indicators	Group	Pre-test Mean±SD	Post-test Mean±SD	Paired-T	Pvalue	Independent-T	P value
LDL-C (mg/dl)	Control	103.8±14.22	104.5±13.41	-1.21	0.25	1.76	0.1
	experience	96.6±6.81	94.6±8.72	1.41	0.19		
HDL-C (mg/dl)	Control	53.8±5.82	54.8±7.19	-0.7	0.49	-2.07	*0.05
	experience	47.3±5.55	52.2±6.71	-3.97	*0.003		
TG (mg/dl)	Control	112.2±27.47	112.9±27.30	-1.65	0.13	3.33	*0.008
	experience	132.1±41.64	112.2±37.99	3.14	*0.012		
Total cholesterol (mg/dl)	Control	183.6±16.4	185.8±12.53	-1.66	0.13	1.53	0.14
	experience	174.3±11.23	173.0±12.99	0.7	0.5		
Glucose (mg/dl)	Control	84.2±5.63	85.2±4.28	-1.26	0.23	1.71	0.115
	experience	94.2±27.55	90.30±20.19	1.42	0.18		
Insulin (mIU/L)	Control	6.74±1.77	5.9±1/00	1.72	0.11	2.23	*0.04
	experience	15.82±4.03	11.77±2.85	2.99	*0.015		
RBP4 (pg/ml)	Control	527.6±442.9	790.2±458.6	-1.18	0.26	2.59	*0.018
	experience	883.3±457.96	374.5±469.23	2.56	*0.03		
Insulin Resistance	Control	1.38±0.27	1.23±0.19	1.64	0.13	2.15	*0.057
	experience	3.76±1.79	2.57±0.59	2.50	*0.034		

* Significance level $\alpha < 0.05$

Discussion

Due to The results of this study, insulin, insulin resistance and RBP4 serum decreased significantly after aerobic exercise.

Obesity increases the RBP4 level in human, while weight loss will reduce RBP4 serum concentrations (12). Studies have shown that RBP4 serum concentration is strongly related to waist circumference, body fat percent, and WHR (17). It was also concluded that training exercises will reduce body fat or will keep the body weight stable (18).

Based on the stated points, a period of aerobic exercise will decrease weight, BMI, WHR, and

body fat percentage. What we concluded in this research proves these benefits. Exercise training increases lipolysis in abdominal subcutaneous fat cells. During endurance exercise, lipolysis of triglycerides in upper body subcutaneous is much greater in comparison to adipose tissue triglycerides. Also, Intra-abdominal adipose tissue lipolysis will increase during exercise (18).

Body composition changes occur after aerobic exercises. This was proved in the current study. According to the research results and relationship between RBP4 with fat percentage, and WHR; after a period of aerobic exercise these variables showed significant differences. That is to say, the significant reduction in the concentration of RBP4

serum is depended on these variables. Endurance exercise increased HDL-c, but decreased triglycerides and individuals with higher levels of aerobic activity or a higher aerobic capacity, have a higher level of HDL-c, but a lower level of triglycerides (19).

Because of the benefits of aerobic exercise; due to increased mitochondrial density, oxidative enzymes in muscle increase. Furthermore, the electron transport chain enzyme activity, the activity of enzymes involved in the oxidation of fats, especially oxidized beta-oxidation cycle enzymes, and also activity of lipoprotein lipase will increase. Increased capacity of fat consumption in the muscles that have been under endurance exercise, is because of their capability to transfer free fatty acids and their increased capacity to oxidize fats.

The decreases in lipids that are because of aerobic exercises are related to weight loss, and decrease in subcutaneous fat. This may happen probably because of a change in metabolic system. An example of change in metabolic system can be lipoprotein enzyme activity which creates lipase (16).

In this study, HDL and triglycerides in the experimental group showed a significant difference that according to the above mentioned statements such results would be expected after a period of aerobic exercise. A study on triglycerides and HDL was carried out with Lim et al. that showed consistent results in the young group. It did not show consistent results in older group people. In other words, the reason for the difference between the older and younger groups in this research can be higher baseline levels of triglycerides and lower HDL level in the older group (15). Insulin resistance and glucose metabolism is usually a gradual process. This gradual process starts by too much weight gain and obesity. Insulin resistance is seen as a key core in metabolic syndrome. Aerobic exercises Improve glucose homeostasis and enhance insulin sensitivity (20). Some of the mechanisms that can improve the insulin task after endurance exercises are: increased insulin signalling receptor, increased glucose transporter protein (GLUT4), glycogen storage capacity due to increased enzyme activity of

synthase glycogen and hexokinase, increased release of glucose from the blood to muscle capillaries due to increased glucose uptake in muscle and changes in muscle composition, and decreased clearance and increased release of free fatty acids (21)

In the current study aerobic exercises decreased glucose, while insulin level decreased significantly. We can conclude that insulin sensitivity increased, insulin resistance decreased and this increase and decrease were significant. Some of the studies have shown that a more decrease in abdominal fat will lead to insulin sensitivity. Fat (especially abdominal) with the production of inflammatory factors may play a key role in insulin resistance and metabolic problems associated with obesity (22). In the present study, WHR, which reflects abdominal fat, was significantly lower in the experimental group, so this may be a factor to explain the reduction in insulin resistance. Exercise enhances insulin function by reducing the intracellular accumulation of triglycerides and fatty acid oxidation (23). In the present study, triglyceride levels were significantly reduced in the experimental group, so perhaps this is another reason for the decrease in insulin levels and insulin resistance in our study. It is important to note that the subjects in the study had a normal glucose level, and this can perhaps be a reason that it did not change significantly. The results with the findings of Rose et al., which worked on the effect of three to four months of aerobic exercise on fasting glucose levels in obese men and women with normal baseline glucose, was consistent. Rose et al. showed that exercise had an Opuscle effect on the fasting glucose level in healthy non-diabetic subjects (24).

In one study, three months of combined activities (aerobic and endurance) showed no significant effect on glucose levels (16), which is consistent with the results of this research. Grout et al., research, Fritz et al., Bloom and Chang studies are inconsistent with the results of the present study (25-27). Lack of a significant effect on insulin resistance perhaps was because of a small number of subjects in the study (25). This may be attributed to the intensity of exercise. In Bloom

and Chang's Investigation, perhaps the reason was intensity and duration of exercise (7 days of moderate-intensity aerobic exercise) (26). Furthermore, the results of the present study are consistent with previous studies (14, 28, 23).

In one study the subjects were postmenopausal diabetic women that were different based on this study. Accordingly, the baseline glucose level was much higher in this study. So perhaps, the reason that glucose level decreased was because of that. It is also shown that the concentration of serum RBP4 is in relation with fasting glucose levels, and improved glucose metabolism after exercise relative to diabetes is the reason that RBP4 level was reduced (6).

In the present study the fasting glucose level was not significant. But, because of the part that RBP4 level is related to insulin level and insulin resistance, perhaps the reason for the significant change in RBP4 level in this study is because of a decrease in insulin level and insulin resistance. The results of the present study are in line with what Choi et al., (2008) concluded. They investigated the relation of combined exercise (aerobic and endurance) in obese women. They did not observe any significant change in the subjects' RBP4 level after three months.

In the study of Lim et al., (2008), aerobic activity with 85-60% insensitivity of VO₂ max, significantly decreased RBP4 level in the older and the younger group. The results of this study are inconsistent with the result in the younger group. The reason for the difference in RBP4 level among the younger groups could be related to the types of subjects. In the present study, obese subjects had significant reductions in body composition due to aerobic exercise. And this significantly decreased the RBP4 level. In Koo et al. study, (2010) the three groups naming control group, endurance training and aerobic training was existed. But, no changes were found in the RBP4 level. Compared to the others in the within group comparison the significant difference was in endurance group (29). Endurance training mainly reduces weight, body fat mass. These trainings will add to bulk but without adding any fat (14), and as it was stated RBP4 serum level has a strong

association with BMI, body fat percentage, waist circumference and it will be decreased by weight loss (3, 8).

Conclusion

The effect of aerobic exercises with the intensity of about 75-50% of pulse with RBP4 index was shown. The results of this study showed the beneficial role of aerobic exercise on metabolic syndrome factors, such as triglyceride, HDL-C, insulin, insulin resistance, and body composition.

It is important to note that more control on some restrictions such as nutritional status of the subjects, emotions, and the number of subjects is necessary for more detailed assessments in further research studies.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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