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Effects of Silymarin Supplementation on Leptin, Adiponectin and Paraoxanase Levels and Body Composition During Exercise: A Randomized Double-Blind Placebo Controlled Clinical Trial

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Abstract

Background: Silymarin has powerful antioxidant properties, but its effects on athletic performance are poorly understood.
Objectives: The present study was undertaken to evaluate the effects of 4 weeks of endurance or strength exercise, with or without silymarin, on body composition, paraoxonase (PON), leptin and adiponectin levels in untrained men.
Methods: A total of 45 untrained men were divided into 5 groups (n = 9): endurance training with placebo (ET + P), endurance training with 140 mg of silymarin/day (ET + S), strength training with placebo (ST + P), strength training with 140 mg of silymarin/day (ST + S) and placebo (C). Anthropometrical and VO_{2max} measurements and ELISA assay for PON, leptin and adiponectin levels were performed at the beginning and after the 4-week of the study
Results: There was a significant decrease in weight and body mass index in the ET + P and ET + S groups and increases in ST + P and ST + S ($P < 0.05$) groups. Body fat declined in all four trained groups ($P < 0.001$). Peak oxygen uptake (VO_{2max}) improved in both ET + P and ET + S subjects. Paraoxonase (PON) was increased only in ET + S group ($P < 0.05$). Adiponectin was increased in all four groups ($P < 0.05$). Circulating leptin remained unchanged within all interventions.
Conclusions: The present study has demonstrated that a combination of exercise and silymarin can improve body composition and adiponectin levels.

Keywords: Exercise, Silymarin, Body Composition, Paraoxonase, Adiponectin, Leptin

1. Background

Maintaining suitable body weight is critical for exercise performance (1). For some athletes, body composition is more important than body weight. In many professional athletes, an increase in body weight is due to an increase in lean body mass rather than body fat. In these cases, using body weight and body mass index (BMI) may result in categorizing muscular athletes as overweight and/or obese. Different kinds of exercise can change body weight and composition in different ways. For instance, high intensity strength training, such as bodybuilding, results in increased strength and lean body mass, with little or no increase in VO_{2max}. In contrast, endurance exercise, such as running, jogging, swimming and cycling, result in elevated VO_{2max} and aerobic fitness without increasing strength or lean body mass (2).

According to previous studies, medicinal plants have numerous health benefits (3, 4). Many animal and human studies have reported that these plants can be useful in some disease and unhealthy conditions (5-8). One of these medicinal plants is silymarin. Silymarin is an antihepatotoxic polyphenolic substance isolated from the milk thistle plant, Silybum marianum. Various preparations of milk thistle, especially the seeds, have been used medicinally for over 2000 years (9). Silymarin has powerful antioxidant properties and a beneficial effect on various hepatic disorders, including alcoholic liver diseases, liver cirrhosis, Amanita mushroom poisoning, viral hepatitis, and toxic and drug-induced liver diseases (10). In addition, many studies have indicated that this herbal medicine has a ben-

eficial effect on diabetic patients and people suffering from cancer (10). Although the therapeutic effects of silymarin on various diseases have been well demonstrated, its effects on athletic performance and athletes' body composition are poorly understood.

Paraoxonase (PON) is associated with high-density lipoprotein (HDL) in human serum, and its activities decline in hypercholesterolemia, diabetes and cardiovascular disease (CVD) (11). Some studies have indicated that exercise can elevate PON activity, as an antiatherogenic agent, which is one of the beneficial roles of exercise in CVD patients (12). On the other hand, many studies do not show significant changes in paraoxonase activity (13).

Adipokines such as leptin and adiponectin are hormones released from the placenta, fetal membranes, adipose tissue and skeletal muscle (14). Both are associated with health status and the metabolism of glucose and free fatty acid. Moreover, acute and chronic exercise affects body composition, carbohydrate and lipid metabolism (15). Theoretically, increase or decrease in body composition can affect the role of adipose and muscular tissue in the secretion of these hormones. Leptin and adiponectin are involved in various biological processes. Leptin is thought to mediate energy balance and body weight through satiety control as well as up-regulating the resting metabolic rate (RMR) and suppressing food intake in humans (16). In contrast to the dramatic increase in plasma levels of several of the adipokines observed in visceral adiposity, the plasma levels of adiponectin are markedly reduced. Thus, adiponectin levels correlate negatively with percent body fat, central fat distribution and fasting plasma insulin (17).

2. Objectives

The present study was undertaken to evaluate the effects of 4 weeks of endurance and strength exercise, with or without silymarin, on body composition, PON, leptin and adiponectin levels in untrained men.

3. Methods

3.1. Study Design and Participants

This study was performed at Islamic Azad University, Ayatollah Amoli Branch, in Amol, Iran, in 2012. The protocol was approved by the local ethical committee of Islamic Azad University, Ayatollah Amoli Branch. The study population consisted of 45 healthy untrained men. A clinical diagnosis of peripheral arterial disease was established using the patients' history and physical examination, and was confirmed by the Doppler assessment of ankle-brachial pressure index (ABPI). The inclusion criteria were limited to non-smoking individuals who had not performed any exercise activity for at least 5 years. Those who had an acute illness or infection; and those who reported a history of inflammatory, cardiovascular and autoimmune disorders; had blood disease; allergy conditions; or had taken any medication within the previous 4 weeks were excluded from the study. In this double-blind study, the subjects were separated into five groups:

1. Endurance training with placebo (ET + P, n = 9),
2. Endurance training with 140 mg of silymarin/day (ET + S, n = 9),
3. Strength training with placebo (ST + P, n = 9),
4. Strength training with 140 mg of silymarin/day (ST + S, n = 9),
5. Placebo (C, n = 9).

3.2. Extraction

For preparing the extract by maceration method, initially 100 grams dried powder of Silybum marianum seeds was weighed and, after milling, was poured into an Erlenmeyer flask. Then, 2 L ethanol (70%) was added to a flask containing the plant and maintained for 48 hours on a shaker at lab temperature. The extract was filtered through filter paper and the pulp was squeezed to discharge. The extract was concentrated using vacuum distillation until the volume was reduced to 20 mL. The concentrated extract was dried (18). The placebo capsules consisted of dextrose.

3.3. Anthropometrical Assessments

Weight ($\pm$ 0.2 pounds) and percent body fat ($\pm$ 0.1%) were measured using the bioelectrical impedance method (HBF-400, Omron, Japan). Body heights were measured to the nearest 0.1 cm, using a standard balance and stadiometer (Seca, Germany). Body mass index (BMI) was calculated with the formula: weight (kg)/height^2 (m^2). All anthropometrical measurements were done in triplicate at 10 seconds intervals, and the mean was calculated for each subject.

3.4. VO2max Measurement

The aerobic fitness level of each soccer player was determined by measuring VO_{2max} (19). The Astrand-Ryhming nomogram (A-R test) was used to predict maximum aerobic power from heart rate elevation at sub-maximum work rates. The A-R test for men requires subjects to step up and down on a 33-centimeter step for 5 minutes at the rate of 22.5 steps per minute. Heart rate was measured from exactly 15 to 30 seconds following completion of the test (20).

3.5. Exercise Protocols

The endurance-training program consisted of running at 60% - 80% of maximal heart rate (HRmax) for 50 [U+200A] minutes per day, 3 days per week, for 4 weeks. The program started with 10 - 15 minutes of running for warm-up, and then continued for 50 minutes of training. Each training session started with a light warm-up and finished with a cool down. The exercise intensity was controlled by the authors, using a heart rate monitor, who ensured that it was between 60 and 80% of HRmax throughout the trial. The training sessions were performed at Islamic Azad University of Amol and were supervised by the researchers.

The strength-training group underwent a 4-week training program, 3 times a week, and commenced with circuit training workout, 3 circuits per session. All subjects were individually supervised and monitored for progress. Eight different exercises designed for the largest muscle groups as one training circuit. The subjects performed a standardized warm-up. For each muscle group, three sets of 10 - 15 repetitions were considered. This program was performed based on a strength training protocol (21). We used the Brzycki equation for predicting maximum repetitions of the bench press.

3.6. Biochemical Measurement

Blood samples were drawn after overnight fasting (12 hours). The blood levels of PON, leptin and adiponectin were determined at the beginning and after 4 weeks of the study in all 5 groups. For serum, blood samples were immediately centrifuged at 4000 g for 15 minutes at 4°C and the serum was aliquoted and stored at -80°C until analysis. The hormonal levels after incubation with human serum were measured using commercially available ELISA kits (Minneapolis, MN USA, 55413).

3.7. Statistical Analysis

All results are presented as mean ± S.D. The data were checked for normality using the Kolmogorov-Smirnov test. A paired sample t-test (for normally distributed variables) and the Wilcoxon test (for non-normally distributed variables) were used to find the significance of changes in all parameters at baseline and after 4 weeks. The SPSS version 16.0 was used for analyzing the data. Significant level was set at $P < 0.05$.

4. Results

Forty-five subjects were recruited, with a median (range) age of 22.7 (18 - 26) years. All of them completed the 4-week intervention. General mean ± SD for all study samples for age (years), weight (kg) and body mass index (BMI, kg/m^2) was (22.7 ± 1.4), (69.2 ± 10.4) and (22.7 ± 3.9) respectively. Table 1 presents these variables for each studied group following the 4-week intervention.

Based on our results, the percentage of body fat decreased significantly ($P < 0.001$) for all four trained groups. These alterations corresponded to changes in body weight. Subjects in both ET groups lost weight over the 4 weeks ($P = 0.001$). On the other hand, subjects in both ST groups gained weight significantly ($P < 0.001$). All ST group subjects gained weight, while 7 of 9 subjects in the ET + P and all ET + S groups lost weight during the intervention period. Along with weight changes, BMI also changed in all trained subjects. In the other words, BMI dropped in the ET groups and rose significantly in the ST groups ($P = 0.001$ for ET+P and ST+S and $P < 0.001$ for ET + S and ST + P).

The VO_{2max} was elevated significantly in groups that performed endurance training (ET + P and ET + S). These changes were about 7.2 and 4.3% for the ET + P and ET+S groups, respectively. No improvement was achieved in participants who performed ST with the placebo or silymarin and in the control group.

Table 2 shows the serum levels of PON, adiponectin and leptin for the subjects of the present experiment following the 4-week intervention. No significant differences were found in PON for the ET + P, ST + P, ST + S and control groups ($P > 0.05$). For the ET+S group, plasma levels of PON were significantly increased following the 4-week study ($P = 0.035$). All 4 trained groups showed a significant increase from baseline in adiponectin throughout the 4-week intervention ($P < 0.05$).

We observed a 38.1% reduction in ET + P subjects, but it was insignificant ($P = 0.083$). While the levels of leptin tended to decrease after 4 weeks, these differences were not statistically significant. On the other hand, basal plasma levels of leptin were not significantly different in the 5 groups after 4 weeks ($P > 0.05$).

5. Discussion

In previous studies, the therapeutic effects of silymarin on some disorders were well documented (10). Despite the many studies conducted, the role of silymarin, as a dietary supplement in athletes is not well defined. The purpose of the current study was to examine the effects of oral consumption of a 140-mg dose of silymarin with or without endurance and strength exercise on plasma levels of leptin and body composition for 4 weeks in untrained males.

Body composition can be affected by different types of exercise. These effects are highly dependent on the intensity of exercise (1). Although our results showed significant changes in all four intervention groups, it seems

Table 1. The Response of Weight, BMI, Percentage of Body Fat and VO_{2max} to 4 Weeks of Exercise, With or Without Silymarin Consumption[a]

	Before	4 Weeks	△ (%)	Intragroup P
Age, y				
ET + P	22.5 ± 1.5			
ET + S	22.8 ± 1.4			
ST + P	22.7 ± 1.5			
ST + S	22.9 ± 1.2			
C	22.8 ± 1.2			
Height, m				
ET + P	1.73 ± 0.06			
ET + S	1.73 ± 0.04			
ST + P	1.75 ± 0.04			
ST + S	1.74 ± 0.05			
C	1.72 ± 0.06			
Weight, kg				
ET + P	70.2 ± 14.8	68.6 ± 15	-2.2	0.001[b]
ET + S	68.6 ± 7.4	66.7 ± 7.0	-2.7	0.001[b]
ST + P	68.7 ± 10.0	69.8 ± 9.5	1.6	< 0.001[b]
ST + S	69.1 ± 7.1	70.2 ± 10.8	1.5	< 0.001[b]
C	70.9 ± 12.3	70.8 ± 12.5	-0.1	0.45
BMI				
ET + P	23.5 ± 3.5	23.0 ± 3.4	-2.1	0.001[b]
ET + S	22.7 ± 2.3	22.1 ± 2.3	-2.6	< 0.001[b]
ST + P	23.6 ± 3.5	23.9 ± 4.0	1.2	< 0.001[b]
ST + S	23.8 ± 3.6	24.2 ± 4.0	1.6	0.001[b]
C	23.9 ± 3.7	23.8 ± 4.1	-0.4	0.479
Body fat (%)				
ET + P	25.1 ± 7.0	22.6 ± 6.2	-9.9	< 0.001[b]
ET + S	22.3 ± 3.7	19.8 ± 3.9	-11.2	< 0.001[b]
ST + P	24.2 ± 6.0	22.7 ± 5.2	-6.1	< 0.001[b]
ST + S	25.8 ± 4.5	23.5 ± 6.4	-8.9	< 0.001[b]
C	25.1 ± 4.5	25.2 ± 4.9	0.3	0.874
VO2 max				
ET + P	34.3 ± 1.2	36.8 ± 1.7	7.2	0.001[b]
ET + S	34.8 ± 1.4	36.3 ± 1.8	4.3	0.020[b]
ST + P	34.3 ± 2.2	34.9 ± 2.0	1.7	0.174
ST + S	33.9 ± 1.8	35.3 ± 2.2	4.1	0.062
C	33.1 ± 1.1	33.3 ± 1.4	0.6	0.731

Abbreviations: ET, endurance training; ST, strength training; P, placebo; S, silymarin; C, control; BMI, body mass index; difference.
[a] Data are expressed as mean ± SD.
[b] P < 0.05.

Table 2. The Response of Plasma PON, Adiponectin and Leptin to 4 Weeks of Exercise, With or Without Silymarin Consumption[a]

	Before	4 Weeks	Δ (%)	Intragroup P
PON, ng/mL				
ET + P	15.94 ± 4.6	16.23 ± 3.9	1.8	0.993
ET + S	14.8 ± 5.7	9.7 ± 3.0	-34.4	0.035[b]
ST + P	14.2 ± 3.9	17.54 ± 5.6	19.0	0.123
ST + S	14.45 ± 4.9	12.71 ± 5.1	-12.0	0.145
C	15.5 ± 5.25	16.3 ± 4.2	5.1	0.386
Adiponectin, pg/mL				
ET + P	124.4 ± 36	151.0 ± 31.8	21.3	0.001[b]
ET + S	120.0 ± 54.3	167.7 ± 64	39.7	0.002[b]
ST + P	123.2 ± 28	151.3 ± 11.36	22.8	0.043[b]
ST + S	159.5 ± 46.9	199.7 ± 57.8	25.2	0.02[b]
C	133.8 ± 39.1	136.1 ± 42.4	1.7	0.92
Leptin, pg/mL				
ET + P	2166.2 ± 192.1	1339.4 ± 112.1	-38.1	0.083
ET + S	1330.9 ± 130	1267.5 ± 174	-4.7	0.765
ST + P	1584.7 ± 103.6	1540.0 ± 119.2	-2.8	0.710
ST + S	1487.6 ± 66.8	1142.5 ± 88.5	-23.1	0.1
C	1463.9 ± 101	1432.1 ± 96.1	-2.1	0.858

Abbreviations: ET, endurance training; ST, strength training; P, placebo; S, silymarin; C, control; PON, paraoxonase; difference.
[a] Data are expressed as mean ± SD.
[b] $P < 0.05$.

that these alternations were due to exercise, not silymarin. On the other hand, there were no differences between endurance (ET + P and ET + S) and strength trained (ST + P and ST + S) subjects in body composition, including weight, BMI and percentage of fat mass (data not shown). These findings are supported in previous studies. Valentova et al. (22) reported that 90 days of supplementation with silymarin had no effect on BMI in patients su [U+FB00] ering from metabolic syndrome. In addition, based on the results of Hajaghamohammadi et al. (23), 140 mg/day silymarin for two months did not change body weight and BMI significantly. In contrast, an animal study showed that short-term consumption of silymarin significantly increased body weight (24).

According to the results for aerobic capacity, VO_{2max} improved in endurance-trained subjects (ET + P and ET + s). There was no significant change in aerobic fitness level in the strength and control groups. It seems that the improvement in VO_{2max} in the ET + S group was due to training, not to silymarin supplementation. This finding supports our previous study (25).

Paraoxonases are a small family of antioxidant enzymes whose antiatherogenic activity is well known (26). They are synthesized in the liver and in serum are located in HDL (27). Several emerging lines of evidence suggest that PON is responsible for the antioxidant properties of HDL on LDL particles (27). The effect of exercise on PON is controversial, and it may be due to the intensity of exercise. Our results showed no significant differences in PON for the ET + P, ST + P, ST + S and control groups. For the ET + S group, plasma levels of PON were significantly increased following 4 weeks of study. Cakmak et al. (28) showed that PON activity was greater in adolescent athletes, suggesting that regular exercise might provide a cardio-protective effect. On the other hand, Romani et al. (26) reported that physical stress, such as acute exercise, by altering membrane composition, may impair PON release from liver membranes and can decrease the level of PON in serum. Moreover, Manresa et al. (13) reported that there is no change of PON activity during exercise.

Adipose tissue secretes adiponectin, an adipocytokine (29) that is inversely related to insulin resistance and hyperinsulinemia. It is hypothesized that increased adiponectin following exercise may be related to changes

in insulin sensitivity (29). Although it was mentioned that exercise could affect adiponectin levels, different studies have shown different results. A cross-sectional study of a male Japanese population investigated whether men who exercise two or more times per week have higher adiponectin levels (> 4 μg/mL) (30). Moreover, in another cross-sectional study of young non-obese women, a positive correlation was found between adiponectin levels and physical activity. In other words, lower physical activity independently predicts lower adiponectin concentrations (31). In contrast, some studies have reported that exercise does not improve adiponectin levels (32). However, both human and animal research has noted that silymarin could improve adiponectin levels (33, 34)). The findings of the present study underline the results of previous studies, demonstrating that 4 weeks of exercise and silymarin can improve circulating adiponectin (33-36).

Leptin is an adipocyte-secreted hormone with a key role in energy homeostasis (37). Leptin plays a central role in the regulation of food intake and energy balance and is strongly correlated with percentage of body fat and to decline after weight loss (37). Some studies have indicated that exercise can alter leptin levels (37, 38). On the other hand, the effect of silymarin on leptin was poorly determined. In an animal study, Loisel et al. (39) reported that leptin concentrations could have been affected by silymarin treatment, but according to our results, there were no significant differences in leptin levels in any of the four trained groups or the control group. These data suggest that a combination of silymarin with exercise endurance or strength does not have any effect on circulating levels of leptin.

In conclusion, we found that endurance or strength exercise combined with silymarin supplementation can improve body composition and adiponectin levels without any changes in leptin levels.

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Footnotes

Authors' Contribution: Study concept and design: Saeid Shirali and Alireza Barari; statistical analysis, interpretation of data and drafting the manuscript: Damoon Ashtary Larky; preparation of the plant and extract: Nafiseh Shokri Mashhadi; acquisition of data: Tahereh Safania.

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