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# Combined effects of aerobic exercises and l-arginine ingestion on total antioxidant capacity (TAC) and C-reactive protein (CRP) in diabetic male rats

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## Abstract:

***Introduction:*** The aim of present study was to investigate the combined effects of aerobic exercises and l-arginine ingestion on total antioxidant capacity (TAC) and C-reactive protein (CRP) in diabetic male rats.

***Material & Methods:*** Analysis method: 24 male rats (age :12 weeks, weight range of 260-360 g) were put randomly into 4 groups of healthy control (n=6), L-arginine supplement consumption group (n=6), aerobic exercise group (n=6) and L-arginine supplement consumption group with aerobic exercise group (n=6).

All of these groups which became diabetic by injection of STZ except the healthy control group were under the study. The aerobic exercise group and L-arginine consumption group and aerobic exercise started walking or running on the treadmill with 10 m/min and slope of 0° for 5 sessions of 15 minutes in a week. After each day, 1 m/min and 5 minutes were added to their exercise and at the end of the seventh day the speed reached to 16 m/min and the time became 45 minutes.

**Results***:* The present results showed that L-arginine supplement consumption made a significant difference between TAC-CRP indicators in supplement and placebo groups. L-arginine supplement consumption made a significant reduction in TAC antioxidant indicator and resulted in CRP increase. TAC antioxidant indicator has an increasing effect on the improvement of total antioxidant capacity of diabetic rats by doing sport exercises but the sport exercises reduce CRP level. Aerobic exercises along with L-arginine supplement consumption didn't change TAC antioxidant indicator of mature rats a lot and are the same in both exercise and without exercise levels but had a significant difference in CRP levels between aerobic exercise-supplement and placebo groups. Exercise reduced significantly on CRP indicator of mature diabetic rats in supplement consumption situation than placebo situation. On the other hand, there was a significant difference between the mean of CRP antioxidant indicator between supplement consumption without exercise and placebo without exercise.

**Conclusions***:* L-arginine supplement resulted in the significant increase of CRP in diabetic mature rats than placebo**.**

**Keywords**: L-arginine, aerobic exercises, diabetes, total antioxidant capacity (TAC), C-reactive protein (CRP).

## 1. Introduction

Researchers and scientists of sport activities always do research in different fields of physical education and sports science, especially sports physiology and its sub-branches, open new windows of science for sports researchers. Determining the physiologic traits and scientific capacities of heroes is one of the important and favorite research topics of researchers and wide dimensions of research is allocated to this field (Agha Hosseini 2008)

These days, the majority of world population live in cities. The modern lifestyles make people to be immobile for physical activities and on the other hand, improper and unhealthy nutrition which mainly contains fatty foods are the factors that cause shorter longevity of human and also metabolic diseases (Iranian diabetes association), one of the most common metabolic disease is diabetes (Iranian diabetes association).

According to the research done so far, more than one million and seventy people worldwide have diabetes that an average of 500000 people is added to these number annually (Iranian diabetes association). According to the last statistics of Iranian diabetes association, five and a half million people have diabetes in Iran that half of them aren't aware of their disease, 13 percent of population over 30 years old in Tehran have diabetes (Iranian diabetes association).

Life continuation with immobility and improper nutrition has made WHO to predict the number of diabetic people from 170 million in 2000 to 366 million people in 2025 (Iranian diabetes association, endocrinology and metabolic office).

Diabetes is a complication due to disorder in insulin production or performance in body (Stamper et al., 1993). If this disease isn't prevented or treated, its side effects can reduce the quality of life in diabetic people and their families and they have a risk of death (Iranian diabetes association, endocrinology and metabolic office).

Generally, the problem that diabetic people have is high blood sugar. Therefore, controlling blood sugar can eliminate their medical problems to the large extent. Currently, the main and effective treatment for

mellitus diabetes is the use of insulin and hypoglycemic drugs, but these structures have various undesirable side effects.

Food supplements are relatively a new topic in sports and it seems that it is the heavy responsibility of sports officials to inform athletes and coaches of the latest information about using sport supplements and drugs and positive and harmful side effects on sport performance and body health in Olympic international committee rule and regulation framework. There have been extensive studies in the field of the effect of food supplements especially vitamins and amino acids on aerobic and anaerobic performance in athletes and non-athletes and various diseases which have contradictory findings in most cases. One of these supplements which used a lot by athletes these days is L-arginine supplement.

According to the positive effects of physical activities on health, exercise and sport physiology have acted to prevent and cure various diseases such as cardiovascular diseases, obesity, diabetes as well as aging and rehabilitation.

Among inflammatory indicators, C-reactive protein with high sensitivity while having high sensitivity, with cheap and available methods can be measured and calculated. Therefore, it is used as a strong independent predicator of cardiovascular disease risk.

Evidence has shown that atherosclerosis is an inflammatory process and the fact that the increase of hs-CRP is associated with the risk of heart attack confirms the relationship between inflammation and atherosclerosis.

All non-enzymatic substances in the blood serum have antioxidant features which is called total antioxidant capacity. These substances protect the body against damages caused by free radicals. Honarmand et.al., (2013) did a research to compare the serum total antioxidant capacity in type 2 diabetic patients and healthy people.

The serum total antioxidant capacity showed a significant reduction in people of the case group compared to control group ($P< 0.001$). There was a reverse relation between the serum total antioxidant capacity and serum glucose concentration in diabetic people and healthy people, but it

wasn't statistically significant in any of those groups. There wasn't a statistically significant relation between serum total antioxidant capacity and people's age.

## 2. Material & Methods

The purpose of doing this research(true experimental) is to Combined effects of aerobic exercises and l-arginine ingestion on total antioxidant capacity (TAC) and C-reactive protein (CRP) in diabetic male rats

The statistical population of this study was totally wistar male rats with 12 weeks old in the weight range of 260-360 grams which were bred in RozhanAzma laboratory animal breeding center.

Among the statistical population, 32 male rats were chosen. Age (month): 3 months, average weight 267 -314 grams.

The rats were kept freely in RozhanAzma laboratory with the temperature of 20-23° C and light- dark cycle of 12 hours (the starts of lightness was 9 a.m. and the start of darkness was 9 p.m.) with 10 rats per rearing cage (control group 8) with standard food and drink. All behavioral tests were done from 10 a.m. to 4 p.m.

Different groups were used as follows:

1. healthy control group
2. diabetic group with STZ and using L-arginine supplement
3. diabetic group with STZ and aerobic exercises
4. diabetic group with STZ, aerobic exercises, and using L-arginine supplement

The process of becoming diabetic with STZ was started a week after adapting to the laboratory environment.

A spectrophotometer machine model S2100SUV was used to measure rats' blood sugar.

Aerobic exercise group and L-arginine supplement user and aerobic exercise group started treadmill with the speed of 10 m/min with 0° slope for 5 sessions each week for 15 minutes every day. After each day, 1 m/min and 5 minutes were added to their exercise and at the end of the seventh day the speed reached to 16 m/min and the time became 45

minutes. L-arginine supplement user group and L-arginine supplement user and aerobic exercise group received 1 g/kg edible L-arginine supplement of their body weight per day for 4 weeks(Shapiro K 2002)

The start of the exercise and L-arginine supplement was taken after48 hours of induction of diabetes in rats' maintenance. At the end, blood samples were taken and antioxidant indicators of TAC-CRP were measured. For rats' blood sample taking after rats' tissue harvest, whole blood was extracted from the animals' heart with syringe after opening their bodies. The blood then was poured in a tube and let them clot in 20 minutes. After this time, tubes were centrifuged at 3000 rpm in 10 minutes, the top serum was taken by sampler carefully and poured into a clean tube and kept in -80° C until the time of the test.

The use of L-arginine was done in a form of oral prescription by using gavage method with edible dose of 1mg/kg.

Serum level: Parso company kit of Elisa method was used to measure CRP concentration.

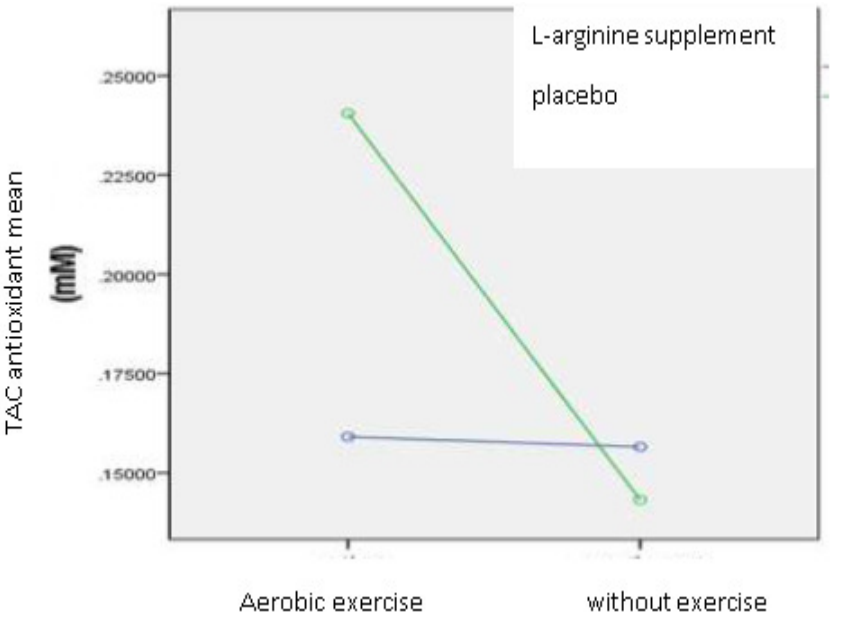
The results of the test were analyzed by Shapiro-Wilk test. To test the hypothesis, two way analysis of variance (ANOVA)were used to compare between exercise × supplement at P>0.05 level.

## 3. Results

The results of two factor analysis of variance has shown that the use of L-arginine supplement has a significant effect on TAC antioxidant indicator of mature male diabetic rats. In other word, the use of L-arginine supplement resulted in the significant reduction of TAC antioxidant indicator of mature male diabetic rats.

Table 1: The results of TAC , two way analysis of variance (ANOVA)

| Row | Source | SS | DF | MS | F | Sig. | |
|---|---|---|---|---|---|---|---|
| **1** | Exercise | 0.015 | 1 | 0.015 | 3.24 | 0.000 | 0.54 |
| **2** | Supplement | 0.007 | 1 | 0.007 | 3.11 | 0.003 | 0.36 |
| **3** | exercise × supplement | 0.013 | 1 | 0.013 | 9.21 | 0.000 | 0.52 |
| **4** | Error | 0.012 | 20 | 0.001 | | | |




TAC antioxidant indicators in research groups

The results of analysis, two-way analysis of variance (ANOVA) in table 1 row 2 showed that the use of L-arginine has a significant effect on TAC antioxidant indicators of mature male diabetic rats. On the other hand, regardless of exercise variable, there was a significant difference between TAC antioxidant indicators of mature male diabetic rats' level in supplement (0.007) and placebo (0.001) groups. In other words, the use of L-arginine supplement caused a significant reduction of TAC antioxidant indicators of mature male diabetic rats.

The results of analysis of two-way analysis of variance (ANOVA) in table 1 row 1 showed that aerobic exercises have a significant effect on TAC antioxidant indicators of mature male diabetic rats. On the other hand, regardless of supplement variable, there was a significant difference between TAC antioxidant indicators of mature male diabetic rats' level in aerobic exercise (0.015) and control (0.001) groups. In other words, aerobic exercises caused a significant increase of TAC antioxidant indicators of mature male diabetic rats.

The results of analysis of, two-way analysis of variance (ANOVA)in table 1 row 3 showed that interactive effect of aerobic exercises and L-

arginine supplement consumption was significant on TAC antioxidant indicators of mature male diabetic rats. In other words, the effect of L-arginine supplement on TAC antioxidant indicators of mature male diabetic rats in aerobic exercise levels (exercise and without exercise) was significantly different. Therefore, the simple effect analysis by using independent t-test with alpha level modification was used to follow the interactive effect.

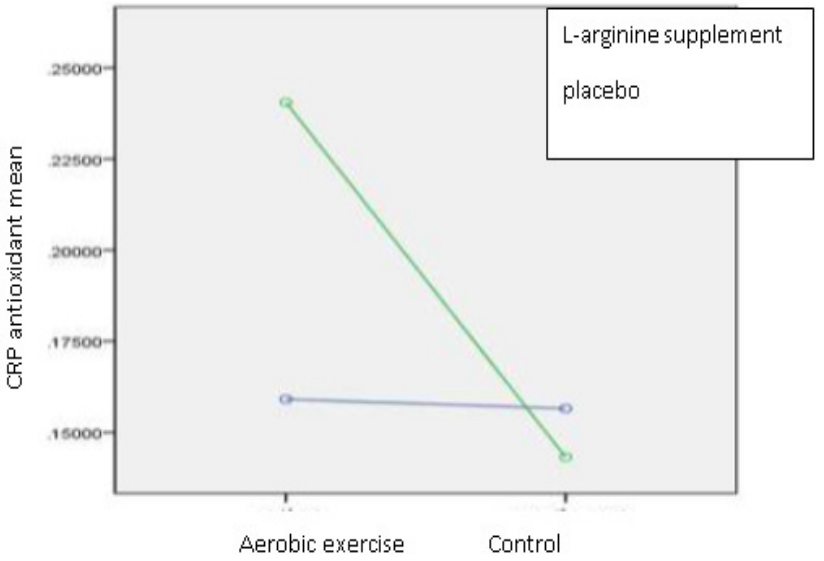
The results of independent t-test showed that there was a significant difference between the mean of TAC antioxidant indicators of mature male diabetic rats in aerobic exercise-supplement group and exercise-placebo group. In other words, the effect of exercise on TAC antioxidant indicators of mature male diabetic rats in supplement consumption situation is significantly less than placebo consumption situation.

The results of independent t-test showed that there wasn't a significant difference between the mean of TAC antioxidant indicators of mature male diabetic rats in supplement consumption-without exercise and without exercise-placebo group. In other words, the effect of supplement on TAC antioxidant indicators of mature male diabetic rats is the same in without exercise situation.

Table 2: The results of CRP, two-way analysis of variance (ANOVA)

| Row | Source | SS | DF | MS | F | Sig. | |
|---|---|---|---|---|---|---|---|
| **1** | Exercise | 1.36 | 1 | 1.36 | 16.89 | 0.000 | 0.89 |
| **2** | supplement | 2.06 | 1 | 2.06 | 27.21 | 0.000 | 0.139 |
| **3** | exercise × supplement | 7.57 | 1 | 7.57 | 80.56 | 0.000 | 0.679 |
| **4** | error | 0.192 | 0.20 | 0.001 | | | |

The results of analysis of, two-way analysis of variance (ANOVA)in table 2 row 1 showed that the aerobic exercise has a significant effect on CRP antioxidant indicators of mature male diabetic rats. On the other hand, regardless of supplement variable, there was a significant difference between CRP antioxidant indicators of mature male diabetic rats' level in aerobic exercise (1.63) and control (0.001) groups. In other words, the aerobic exercise caused a significant reduction of CRP antioxidant indicators of mature male diabetic rats.




CRP antioxidant indicators in research groups

The results of analysis of two-way analysis of variance (ANOVA) in table 2 row 2 showed that the use of L-arginine has a significant effect on CRP antioxidant indicators of mature male diabetic rats. On the other hand, regardless of exercise variable, there was a significant difference between CRP antioxidant indicators of mature male diabetic rats' level in supplement (2.60) and placebo (0.001) groups. In other words, the use of L-arginine supplement caused a significant increase of CRP antioxidant indicators of mature male diabetic rats.

The results of analysis of two-way analysis of variance (ANOVA) in table 2 row 3 showed that interactive effect of aerobic exercises and L-arginine supplement consumption was significant on CRP antioxidant indicators of mature male diabetic rats. In other words, the effect of L-arginine supplement is significantly different on CRP antioxidant indicators of mature male diabetic rats in aerobic exercise levels (exercise-without exercise). Therefore, the simple effect analysis by using independent t-test with alpha level modification was used to follow the interactive effect.

The results of independent t-test showed that there was a significant difference between the mean of CRP antioxidant indicators of mature male diabetic rats in aerobic exercise-supplement group (4.23) and exercise-placebo group (4.71) (P=0.000). In other words, the effect of exercise on CRP antioxidant indicators of mature male diabetic rats in supplement consumption situation is significantly less than placebo consumption situation.

On the other hand, the results of independent t-test showed that there was a significant difference between the mean of CRP antioxidant indicators of mature male diabetic rats in supplement consumption-without exercise (5.89) and without exercise-placebo group (4.09). In other words, L-arginine supplement without exercise resulted in a significant increase of CRP antioxidant indicators of mature male diabetic rats than placebo consumption without exercise.

In simpler terms, supplement in exercise situation caused a significant reduction in CRP antioxidant indicators of mature male diabetic rats, but in without exercise situation caused a significant increase in CRP antioxidant indicators of mature male diabetic rats.

## 4. Discussion

The results of the present study showed that the serum non-enzymatic antioxidant levels in Esterpetoztoysen -induced diabetic rats had a significant reduction but after the injection of L-arginine in edible form and doing sport exercises and supplementation and doing exercises, antioxidant capacities of diabetic rats increased significantly that this increase was more in group which did saffron supplementation and exercise simultaneously and their serum antioxidant levels reach to the amount of healthy control rats.

It seems that, diabetes is associated with many autoimmune diseases and causes some disorders in electron transfer chain and finally, increases the free radicals resulted from oxidative stress and reduces blood antioxidant amount at the same time. The increase of oxidative stress is a well-accepted special factor in completion and progression of diabetes and its side effects. Diabetes is usually associated with the increase of free radicals' production or defensive destruction of body antioxidants.

Mechanism by which oxidative stress is increased by diabetes are partly known and includes activation of transcription factors, advanced glycolysis final products and C-kinase protein. The results of some research have also suggested that the beta cells' performance is impaired as a result of long exposure to high levels of glucose and free fat acids or the mixture of both. In particular, beta cells are sensitive to reactive oxygen types since their capacity is low in antioxidant enzymes of free radical such as catalase, peroxidase glutathione and dismutase superoxide.

The results of the present study were consistent with the results of some studies and showed that by the spread of diabetes and disruption of production and secretion of insulin hormone, disorders take place in other body systems and antioxidant capacity decreases specifically in body.

Exercise is associated with the increase of free radical formation which is mainly arising from the increase in O2 consumption by active tissues. Several studies have shown that the number of free radicals in biological tissues have increased after the acute or chronic exercise which is along with the presence of destruction in blood components or tissues. Most of used O2 is used for aerobic phosphorylation in mitochondria and changes into water. Anyway, less but significant reduction in used O2 may cause the electron transfer chain to produce ROS and it is estimated that about 2-5% of used oxygen changes to free radicals by mitochondria. Chronic exercise with average intensity changes cells and tissues' homeostasis positively by reducing the basic levels of oxidative damage and increase of resistance to oxidative tension. In fact, regular exercise makes adaptations in antioxidant capacity and protect cells against oxidative stress harmful effects and therefore, prevent cell destruction.

Oxidative stress is usually a reason for pathology of observed micro and macro vascular disease in diabetic people. Some information supports the role of regular exercise in reduction of peroxidation lipid. Instead, if the regular exercise can show a supportive effect against oxidative stress in tasteless diabetes, it is more interesting to use them as non-pharmaceutical treatments for type 2 diabetes. Observed cardiovascular adaptations because of regular exercise include not only blood pressure

reduction but also accumulation and adhesion of platelets and heart blood flow increase. This adaptation may be at least partially maintained by the over-regulation of basal nitric oxide (NO) product. Along with this idea, there is the report of an increase in NO products along with a decrease in blood pressure and platelet activity in people who do long-term exercises. Enhancement of observed produced NO during acute exercise is able to induce protective adaptations by interaction with various transcription factors and, consequently, affecting the expression of oxidant enzyme genes. Although the nature of antioxidants is attributed to uric acid; high level of uric acid is strongly related and in many cases is predictive of the development of hypertension, visceral obesity, insulin resistance, type 2 diabetes, kidney disease, and cardiovascular events.

It seems that regular physical activity protect human against obesity and premature death. Several studies have investigated the role of regular physical activity in cardiovascular and metabolic abnormalities involved in diabetes. However, the results of these animal studies cannot be applied directly to humans, animal specimens with diabetes can provide an excellent opportunity to assess experimental conditions and tissues that cannot be tested in humans, and to increase our knowledge of endocrinology, metabolic and morphological changes related to pathogenic mechanisms and treatment options. In previous studies, Kretschmar et al. (1991) reported an increase in plasma glutathione after doing resistance exercise in human specimens. The results of Mena et al.'s study (1991) confirmed the effect of an increasing sport exercise on the improvement of erythrocyte antioxidant enzymes activity. Also, the results of most studies performed on samples of laboratory organisms, including mice, unanimously show an improvement in the activity of antioxidant enzymes in muscles. Although there have been conflicting studies on the effect of sport exercise on the activity of non-enzymatic serum antioxidants, but this is showed in previous studies that sport exercise increases the total antioxidant capacity of the body, and we can say that the results of the present study confirmed the findings of previous studies about the increased activity of antioxidants. The results of some studies showed that the weight of some organs or tissues (heart, liver, kidneys and muscles) increased in diabetic rats that did the

exercise which is the indicator of the effect of exercise on morphological and physiological adaptations to maintain homeostasis. The results of Tamilto et.al., (2001) showed that exercising more than 4 hours per week without changing the weight of the subjects reduces the potential for diabetes significantly.

Given that exercise which includes components designed to improve cardiovascular fitness and muscle strength, studies have shown that more than 4 hours of exercise per week, even without weight loss, is associated with a significant reduction in the risk of diabetes. Some of the beneficial effects of an exercise program include visceral fat reduction and muscle mass increase. Random controlled periods in individuals with body mass index (BMI) as well as in patients with abdominal obesity and type 2 diabetes showed that regular physical exercise reduced total visceral and subcutaneous fat, even without weight loss, with glycemic improvement and increased free fatty acids oxidation and thus diabetes improvement. According to human studies in a meta-analysis study in which the performed studies were related to exercise interventions with at least eight weeks in type 1 and 2 diabetics, regular aerobic exercise showed a statistically and clinically significant effect on HbA1c and suggested Non-pharmacological interventions improve glycemic control while having little effect on body weight. Similar results have been reported from the effect of exercise from another meta-analysis study which included 14 studies (12 aerobic exercises and 2 resistance exercises) and showed a positive effect of exercise on HbA1c (the main indicator of glycemic control).

Research limitaioms: dead of two rats in 9 week

## 5. Conclusion

The results of the present study showed that L-arginine supplement consumption showed a significant difference between the TAC-CRP antioxidant index between the supplement and placebo groups. Consumption of L-arginine supplement reduced the TAC antioxidant index significantly and led to the increase of CRP. Sport exercises have increasing effect on TAC antioxidant indicator in the improvement of total antioxidant capacity in mature rats, but they reduce CRP level.

Aerobic exercise along with L-arginine supplement consumption didn't change TAC antioxidant indicator in mature diabetic rats and was the same in exercise and without exercise levels but made a significant difference in CRP levels between aerobic exercise-supplement and exercise placebo. Exercise had a significant reduction on CRP indicators of mature diabetic rats in supplement consumption situation than placebo consumption situation. On the other hand, there was a significant difference between the mean of CRP indicator between supplement consumption group without exercise and placebo group without exercise. L-arginine supplement without exercise caused a significant increase in CRP of diabetic rats than placebo. Diabetic patients can use L-arginine supplement as it reduces the time of wound healing, helps allergy increase and insulin performance, improves and reinforces body immune system and L-arginine reduces blood pressure as well. Sport exercise is useful for diabetic patients because immobility results in weight gain and acute diabetes.

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