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Changes in Some Observational Cardiac Parameters and Cardiac PGC1-α Expression Following Eight Weeks of Endurance Training and Saffron Consumption in Animal Models of Alzheimer's Disease

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Abstract

Introduction: The link between Alzheimer's disease (AD) and heart disease has recently been reported. Previous studies have reported the beneficial role of endurance training (ET) and saffron (Sa) on the heart and nervous system health, but their interactive effect is not yet well known. Therefore, the aim of this study was to determine changes in some observational cardiac parameters and cardiac PGC1-α expression after 8 weeks of ET and Sa consumption in animal models of AD.

Methods: In this experimental trial, 40 rats with AD (by intraperitoneal injection of 8 mg/kg neurotoxin trimethyltin) were divided into (1) AD, (2) sham (Sh), (3) Sa, (4) ET, and (5) ET + Sa groups. Additionally, to evaluate the effect of AD induction on the research variables, 8 healthy rats were included in the healthy control (HC) group. Groups 4 and 5 ran for 8 weeks, three 15-30 minute sessions per week at a speed of 20-15 m/min. Groups 3 and 5 received 25 mg/kg aqueous extract of Sa peritoneally each day. To analyze the data, dependent samples *t* test, one-way analysis of variance and Tukey's post hoc test, analysis of covariance with Bonferroni's post hoc test in SPSS version 22.0 were used ($P \geq 0.05$).

Results: In the Sa and ET + Sa groups, heart weight, heart weight to body weight ratio, and cardiac PGC1-α expression were higher and the body weight of these groups was significantly lower compared with the AD group ($P \leq 0.05$). Moreover, in the ET group, heart weight was higher than body weight and total body weight was lower compared to the AD group ($P \leq 0.05$).

Conclusion: It seems that Sa and ET + Sa interaction improve heart function and some parameters related to heart health by increasing PGC1-α expression, but the effect of training depends on its type and intensity, which should be further studied.

Keywords: Endurance training, Crocus sativus, PGC1-α, Heart, Alzheimer's disease

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Introduction

Today, with increasing life expectancy and longevity, the elderly population is increasing, and this is associated with an increased risk of heart and psychological diseases such as Alzheimer's disease (AD).[1] Weight gain, metabolic disorders, organ failure, and decreased physical activity expose the elderly to heart disease and cognitive impairment, so myocardial infarction and AD are directly related.[1,2] The incidence of myocardial infarction in patients with AD is reported to be about 20% to 45% higher compared to the elderly.[2] Defects in heart cell regeneration, disorders of the sympathetic and parasympathetic nervous systems, disorders of neurotransmitters, decreased synthesis of vital cell proteins, and increased oxidative stress in these patients are important causes of cardiovascular disease.[3] Given that mitochondria play an important role in cell life, interventions and activating proteins of this organelle such as peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 α (PGC1α) cause mitochondrial

biogenesis, reduce oxidative stress, improve metabolism, reduce fat, decrease body mass index, and reduce risk of heart disease.[3,4] Considering the increasing prevalence of cognitive and metabolic disorders in the elderly population, it is important to provide them with effective treatment strategies. Therefore, the positive role of exercise training in improving cognitive function,[5] improving balance and muscle strength,[6] reducing inflammatory factors in skeletal muscle tissue,[7] reducing oxidative stress in cerebral arteries[8] and improving cardiac function has been reported in AD patients.[9] Exercise training with the mechanism of increasing cyclic adenosine monophosphate (cAMP) leads to the phosphorylation of protein kinase A (PKA), and activation of protein kinase activated by cAMP (AMPK) leads to the phosphorylation of PGC1α, increased nuclear transcription, mitochondrial proliferation, recovery of substrate metabolism in skeletal and cardiac muscle, and ultimately weight loss.[10] In this regard, 4 weeks of swimming training increased PGC1α and hypoxia-inducible factor 1α (HIF-1α) in rat heart. Exercise increased oxidative capacity and PGC1α expression in 24-month-old rat muscle.[11] In addition to regular physical activity, the role of medicinal plants with antioxidant properties along with exercise has been considered by researchers in the field of sports science.

Saffron (Sa) is composed of crocin, crocetin, safranal, and picrocrocin with anti-inflammatory, anti-diabetic, anti-hypertensive, anti-cancer, and antioxidant properties, which is used in the treatment of many diseases including cognitive disorders, anxiety, depression, and AD and improvement of fat metabolism, reduction of appetite, and weight loss.[12] In this regard, the consumption of Sa and its active ingredients increases the expression of PGC1α, reduces oxidative stress in the brain tissue of rats with AD,[13] and increases the expression of PGC1α in the heart tissue of rats with type 2 diabetes.[14] Although there is useful information about the effect of exercise and Sa on the treatment of diseases, due to the prevalence of common heart disorders in patients with AD, it seems necessary to discover new solutions that can show the simultaneous effect of exercise and crocin. Therefore, the present study aimed to determine changes in weight and cardiac PGC1-α expression after 8 weeks of endurance training (ET) and Sa consumption in animal models of AD.

Materials and Methods

In this experimental trial, 48 eight-week-old male Sprague Dawley rats weighing approximately 220 ± 30.65 g were prepared and transferred to the Animal Laboratory of Sports Physiology of Islamic Azad University, Marvdasht Branch. The animals were kept in the laboratory for 1 week for adaptation. During the protocol period, rats were kept in standard conditions in terms of temperature (22-24°C), dark-light cycle (12-12 hours), and relative humidity (55% to 65%) in washable cages. The animals also had access to water and food ad libitum during the study. It is noteworthy that all the ethical principles of working with laboratory animals were observed under the supervision of the Ethics Committee for Working with Laboratory Animals of the Islamic Azad University, Marvdasht Branch, which was developed based on the Helsinki Declaration. After one week of adaptation, 8 mg/kg neurotoxin trimethyltin (Sigma, Germany) was injected intraperitoneally to induce AD in 40 rats. To diagnose AD in rats, 14 days after injection, shuttle box and maze tests were performed to assess memory and learning.[15] Then, rats with AD were divided into 5 groups of 8, including: (1) AD control, (2) ET, (3) Sa consumption, (4) ET + Sa, and (5) sham group (crocin solvent). To evaluate the effect of trimethyltin on the research variables, 8 healthy rats were placed in the healthy control (HC) group. The ET and ET + Sa groups ran on a rat treadmill for eight weeks, three 15-30 minute sessions per week at a speed of 15 to 20 m/min.[16] Moreover, the Sa and ET + Sa groups received 25 mg/kg aqueous extract of saffron dissolved in normal saline intraperitoneally each day.[17]

Measuring Research Variables

About 100 mg of each tissue sample was mixed with 750 µL of TRIzol solution (Yekta Tajhiz Co., Iran) and then homogenized. Then, RNA was extracted using the protocol of the manufacturer (Sinagen, Iran). After extracting the RNA, its quantity and quality were measured by spectrophotometry and optical absorption was determined at 260 nm. A260/A280 ratio was calculated to determine the purity of RNA. After extraction of RNA with very high purity and concentration from all studied samples, cDNA synthesis was performed according to the protocol of the manufacturer (Biofact, South Korea) and then the synthesized cDNA was used for reverse transcription reaction.

First, the primers designed were examined using the NCBI database (main gene and internal control gene), and then gene expression was examined using quantitative real-time PCR. Table 1 provides information on the primers used in the study. After completing the operation of the device and viewing the diagrams, the $2^{-\Delta\Delta CT}$ formula was used to quantify the data.

Data Analysis

Dependent samples *t* test was used to examine pre-test

Table 1. Sequence of Primers Used in This Study

Gene	Primer Sequence
PGC1-α	F5´TTCAGGAGCTGGATGGCTTG3´
	R5´AGATCTGGGCAAAGAGGCTG3´
GAPDH	F:5´AGTGCCAGCCTCGTCTCATA3´
	R:5´GAGAAGGCAGCCCTGGTAAC3´

and post-test weight changes, and analysis of covariance with Bonferroni's post hoc test was used to examine post-test weight changes by eliminating the pre-test effect. Furthermore, one-way analysis of variance with Tukey post hoc test was used to evaluate the differences between groups in the variables of heart weight, heart weight to body weight ratio, and PGC1-α expression in SPSS version 22.0 ($P \leq 0.05$).

Results

The results of dependent samples *t*-test showed that the post-test weight of the HC ($P=0.003$) and Sh ($P=0.001$) groups increased compared to the pre-test weight and the post-test weight of the ET + Sa ($P=0.001$) and ET ($P=0.002$) groups was significantly lower compared to the pre-test weight.

The results of one-way analysis of variance (ANOVA) showed a significant difference in PGC1-α ($P=0.001$), heart weight ($P=0.001$), and heart weight to body weight ratio ($P=0.001$) in the research groups. The results of the analysis of covariance to eliminate the effect of pre-test weight showed a significant difference in the post-test weight in the research groups ($P=0.001$).

The results of Tukey post hoc test showed that PGC1-α gene expression levels in the AD group were significantly lower compared to the HC group ($P=0.014$). There was also no significant difference between the AD and Sh groups ($P=0.45$); however, in the Sa ($P=0.001$) and ET + Sa ($P=0.001$) groups, PGC1-α gene expression level was significantly higher compared to the AD group, but no significant difference was observed in the AD and ET groups ($P=0.68$). Besides, in the Sa ($P=0.001$) and ET + Sa ($P=0.001$) groups, PGC1-α gene expression level was significantly higher compared to the ET group (Figure 1).

Heart weight in the AD group was significantly lower compared to the HC group ($P=0.001$). Moreover, in the Sa ($P=0.001$) and ET + Sa ($P=0.001$) groups, it was significantly higher compared to the AD group, but no significant difference was observed in the ET and AD groups ($P=0.086$) (Figure 2).

Heart weight to body weight ratio in the AD group was significantly lower compared to the HC group ($P=0.01$), but no significant difference was observed in the AD and Sh groups ($P=0.050$); however, heart to body weight ratio in the Sa ($P=0.001$), ET ($P=0.026$), and ET + Sa ($P=0.001$) groups was significantly higher compared to the AD group (Figure 3).

The results of Bonferroni's post hoc test showed that by eliminating the pre-test effect, no significant difference was observed in the weight of AD and HC groups ($P=0.99$) Additionally, no significant difference was observed in the AD and Sh groups ($P=0.99$). However, in the Sa ($P=0.006$), ET ($P=0.001$), and ET + Sa ($P=0.001$) groups, the weight was significantly lower compared to the Sh group (Figure 4).

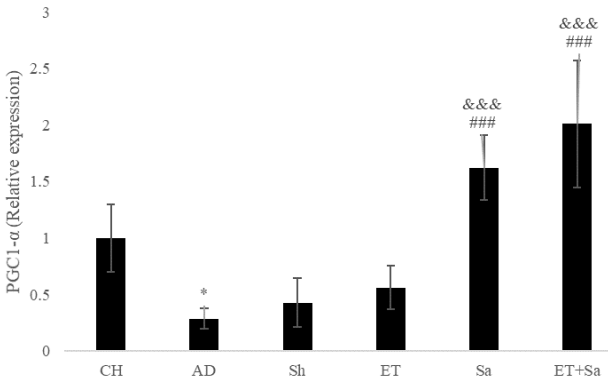

Figure 1. PGC1-α Gene Expression Levels in the Heart Tissue of Rats in the Study Groups. * ($P=0.05$) Significant decrease compared to the HC group; ### ($P=0.001$) Significant increase in the Sa and ET + Sa groups compared to the AD group; &&& ($P=0.001$) Significant increase in the Sa and ET + Sa groups compared to the ET group

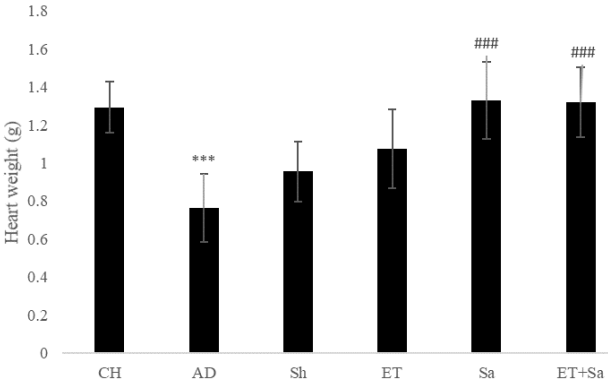

Figure 2. Heart Tissue Weight of Rats in the Study Groups. *** ($P=0.001$) Significant decrease compared to the HC group; ### ($P=0.001$) Significant increase in the Sa and ET + Sa groups compared to the AD group

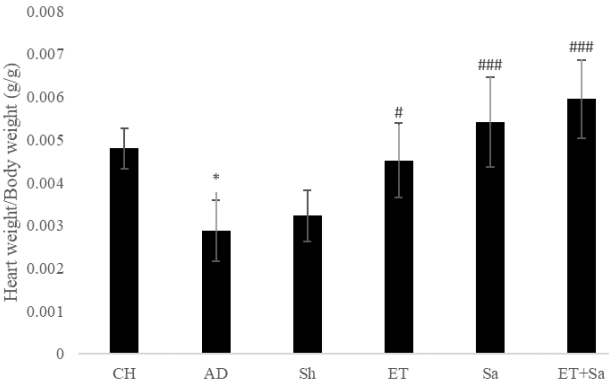

Figure 3. Heart Tissue to Total Body Weight Ratio of Rats in the Study Groups. * ($P=0.05$) Significant decrease compared to the HC group, ###($P=0.001$) and # ($P=0.05$) significant increase in the Sa, ET + Sa, and ET groups compared to the AD group

Discussion

The results showed that ET increased heart weight to body weight ratio and decreased weight, but it had no

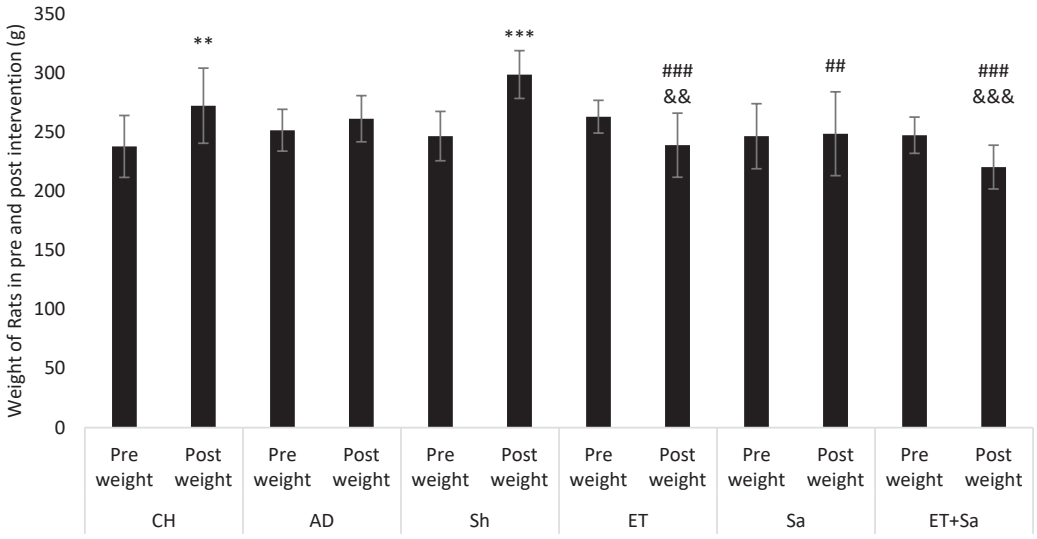

Figure 4. Pre-test and Post-test Weight of Rats in the Study Groups. *** ($P=0.001$) and ** ($P=0.01$) Significant increase in the pre-test weight in the CH and Sh groups; &&& ($P=0.001$) and && ($P=0.01$) Weight loss compared to the pre-test body weight in the ET and ET + Sa groups; ### ($P=0.001$) and ## ($P=0.01$) Significant decrease in the post-test weight in the ET, Sa, and ET + Sa groups compared to the Sh group

significant effect on PGC1-α expression and heart weight in rats with AD.

Consistent with the present study, running for 8 weeks, three 15-30 minute sessions per week at a speed of 1.2 km/h and 0.8 km/h reduced inflammatory factors in the skeletal muscle tissue of rats, but had no significant effect on the increase of PGC-1α in middle-aged rats.[18] In addition, 6 weeks of high-intensity and low-intensity interval training did not increase PGC-1α protein levels in the heart tissue of rats with myocardial infarction, but moderate-intensity interval training increased PGC-1α expression.[19] On the other hand, 12 weeks of endurance swimming increased the levels of PGC1-α, AMPK, SIRT1, and FOXO3a in the skeletal muscle of 3-, 12- and 18-month-old rats.[20] In another study, 4 weeks of swimming training increased PGC1α expression in the heart tissue of rats.[21] Besides, moderate-intensity aerobic training increased oxidative capacity and PGC1α expression in the muscle tissue of 24-month-old rats.[11] Therefore, the role of exercise training intensity in increasing PGC-1α expression is important, and it seems that the intensity of training in this study was not sufficient to increase the expression of this protein. The risk of developing AD, Parkinson's disease, Huntington's disease, and multiple sclerosis increases with age. Disorders in the sympathetic and parasympathetic nervous systems, spinal nerves, and vagus nerve are associated with Purkinje dysfunction, increased heart rate, hypertension, and myocardial infarction.[22] Dysfunction of acetylcholine, epinephrine, and norepinephrine following AD leads to impaired Ca^{2+}transmission, impaired sodium/potassium channel function, adenosine triphosphate (ATP), ATP/ADP ratio, mitochondrial dysfunction, and impaired PGC1-α expression.[23] Impaired PGC1-α expression leads to increased reactive oxygen species and decreased antioxidants and the energy level of heart cells and exposes the person to weight gain, increased fat mass, pathological heart hypertrophy as well as heart attack.[24] However, aerobic exercise with the mechanism of improving the function of neurotrophins, improving the function of the nervous system, and increasing catecholamines through beta-adrenergic receptors leads to an increase in cAMP. Additionally, by phosphorylation of protein kinases to nuclear respiratory factors, PGC1-α, and the mitochondrial transcription factor A, it increases the number and volume of mitochondria and ultimately improves the metabolism of energy substrates in the cell, resulting in reduced fat mass, white-to-brown fat conversion, weight loss, and inhibition of pathological cardiac hypertrophy.[5,9,11]

The results showed that Sa increased the PGC1-α gene expression level in heart tissue, heart weight, and heart weight to body weight ratio and decreased weight in rats with AD. Consistent with the present study, Sa supplementation led to weight loss and fat loss and improved fat profile in overweight women in another study.[25] Additionally, Sa supplementation also increased PGC1-α gene expression level in the hippocampal tissue of AD rats.[26] In another study, the use of crocin as an active ingredient of Sa caused a relative improvement in aerobic capacity and reduced anxiety-like behaviors in rats with AD.[13] On the other hand, consumption of 25 mg/kg crocin had no significant effect on weight loss, calorie intake, and aerobic capacity in rats with type 2 diabetes.[27] Regarding the metabolic disorders of obesity and type 2 diabetes in this study and the dysfunction of the nervous system in the present study, the difference in the statistical population and the type of disorder should be further investigated. Sa and its constituents through enzymatic and non-enzymatic antioxidant

pathways reduce the gene expression level of nuclear factor kappa-B (NF-κB), interleukin-1 beta (IL-1β), and tumor necrosis factor α (TNF-α), increase neurotrophins, the *cAMP-response element binding* (CREB) protein, and vascular growth factor (VGF), and modulate the vagus, gabaergic, sympathetic, and parasympathetic nervous systems.[28] In addition, by regulating calcium channels and activating calcium-calmodulin channels, Sa activates FOXO pathways and nuclear gene transcription, increases PGC1-α expression and mitochondrial biogenesis, fat lipolysis, insulin sensitivity as well as weight loss, and improves cell metabolism.[13,25]

The results showed that ET + Sa increased the levels of PGC1-α gene expression in the heart, heart weight, as well as heart weight to body weight ratio and decreased weight in rats with AD. In this regard, continuous training and Sa consumption improved fat profile, reduced fat mass, and increased the level of irisin and visfatin in overweight women.[25] In addition, aerobic training and crocin consumption increased PGC1-α gene expression level in the hippocampus and increased aerobic capacity in rats with AD.[13,26] However, interval and continuous training along with crocin consumption did not have an interactive effect on calorie intake in rats with type 2 diabetes but it caused weight loss.[27] Exercise training, depending on the type and intensity of activity, has different effects on the biological pathways of the cell. Although studies show the positive effect of physical activity on the activation of the PGC1-α gene expression pathway, proper adaptation occurs after long-term training in response to oxidative stress in each training session; therefore, the activation of biological pathways following exercise, especially the PGC1-α pathway, depends on the type and intensity of training.[5,9,11,20] Furthermore, Sa plant, with enzymatic and non-enzymatic antioxidant mechanisms, reduces NF-κB, IL-1, and TNF-alpha, increases BDNF, CREB, and VGF, regulates calcium channels, activates calcium-calmodulin and FOXO, improves neurotransmitters functions, regulates cell ion function, and increases PGC1-α, mitochondrial biogenesis, insulin sensitivity and weight loss.[25,26,28] Due to changes in heart weight and heart weight to body weight ratio, which require more pathological and physiological examination, one of the limitations of the present study is the lack of examination of pathological changes in the heart. Therefore, it is suggested that pathological examination be evaluated in future studies. Due to the insignificance of PGC1-α levels in the heart tissue of rats with AD, it seems that the intensity training, different pathways of adaptation to training, as well as conditions related to metabolic disorders have an effect on these results. Therefore, it is suggested that different intensities of training be evaluated in future studies.

Conclusion

It seems that Sa consumption and training and Sa consumption interaction with the mechanism of increasing PGC1-α improve heart function and some parameters related to heart health in neurodegenerative disorders such as AD. However, the effect of training depends on its type and intensity, which needs to be further studied.

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Authors' Contribution

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Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The present study was approved by the Ethics Committee of the Sports Sciences Research Institute of Iran (Code: IR.IAU.M.REC.1399.004).

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