Original Article

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High-Intensity Interval Training Combined with Saffron Supplementation Modulates Stress- Inflammatory Markers in Obese Women with Type 2 Diabetes

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Abstract

Introduction: The aim of this study was to investigate the interactive effects of saffron extract supplementation with high-intensity interval training (HIIT) on serum levels of stress-inflammatory markers in obese women with type 2 diabetes.

Method: Thirty-two obese women with type 2 diabetes were randomly divided into 4 intervention groups: supplement, HIIT +Supplement, placebo and placebo + HIIT. The anthropometric and blood characteristics of subjects were evaluated in pre-test and post-test. The method of supplementation was that the supplement group received 100 mg of saffron extract daily. The subjects in the training group also did running on the treadmill in 4 bouts with intensity of 85 to 95% of the maximum heart rate along with 4 periods of active rest at the intensity of 50 to 60% of the maximum heart rate.

Results: Data analysis showed that the effect of time was a significant decrease in serum levels of IL-6, NT-proBNP, and GDF-15 in the supplement, supplement + HIIT +, and placebo + HIIT groups ($P \leq 0.05$). The results of time × group interaction also showed a significant difference between the groups ($P \leq 0.05$). So that the decrease in the levels of stress-inflammatory markers in the supplement + HIIT group had a greater decrease.

Conclusion According to the results, it can be reported that HIIT and saffron supplementation (combination of both) probably reduces the levels of stress-inflammatory markers such as GDF-15, NT-proBNP, and IL-6 by reducing fat mass, as well as also improve glucose metabolism and insulin resistance in obese women with diabetes.

Keywords: Growth differentiation factor-15, interleukin-6, NT-proBNP, inflammation, type 2 diabetes.

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1. Introduction

Type 2 diabetes (T2DM) is a metabolic disease that causes hyperglycemia (hyperglycemia) by impairing insulin secretion, reducing insulin sensitivity, or increasing insulin resistance(1), which can cause a reaction. Inflammatory, metabolic, and cardiovascular diseases, followed by an increased risk of disease and mortality(2). Therefore, blood glucose control is one of the cornerstones of treatment in people with type 2 diabetes(3). In addition, diabetes is one of the main risk factors for heart failure (HF), which is associated with an increased risk of more than 50% and has substantial adverse effects on HF prognosis (4). Heart failure is also the second most common symptom of cardiovascular disease (CVD) in patients with type 2 diabetes and is more common than myocardial infarction (5). However, insufficient emphasis has been placed on the prevention and treatment of heart failure in the clinical control of diabetes (6).

Several circulating biomarkers have recently been shown to be associated with CVD, such as C-reactive protein (CRP), interleukin-6 (IL-6), and pro-BNP natriuretic peptide (NTpro-BNP), and growth differentiation factor-15 (GDF-15) (7). It has also been suggested that these biomarkers help predict the risk of heart failure. However, few studies have examined the association between these biomarkers and the risk of heart failure in diabetic patients, and it is unclear to

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what extent these biomarkers can classify the risk of heart failure in such patients.

In response, traditional and emerging medication strategies and lifestyles such as physical activity and diet continue to be considered to reduce the burden of these metabolic disease conditions (8, 9). The American Diabetes Association (ADA) recommends at least 150 minutes a week of moderate to vigorous physical activity or 75 minutes a week of vigorous physical activity for everyone (8, 9). However, inactivity and lack of perceived time are the main reported reasons for not exercising regularly(10, 11). Many people today use new exercise training regimens such as high-intensity interval training (HIIT) with active intervals (30 seconds and 4 minutes) with active rest intervals. On the other hand, the cost-effectiveness of this type of exercise in terms of time, as well as similar metabolic and physiological adaptations (12-14) and sometimes superior (15, 16) of this type of exercise compared to continuous moderate-intensity training (MICT) causes It has become increasingly popular.

On the other hand, nowadays, they are active food compounds or dietary supplements that have been proven to have benefits beyond basic nutritional functions, including health promotion through treatment and prevention of diseases (17), which is a factor in various components of plants such as flowers, There are roots in plants and oils called "nutrients" (18). Saffron is a short-lived plant that is found in various parts of the Mediterranean, Europe, and Asia (19). Saffron is used as a spice due to its coloring, flavoring, and aromatic properties (20). Crocus sativus contains crocetin, crocin, pyrocrocin, and safranal which are effective in regulating inflammation and oxidative stress (21). In line with the anti-inflammatory properties of saffron, it can also be said that saffron prevents the activation and release of kappa nuclear factor activated B-cell light chain (NF-kB) and prevents the transfer of NF-kB to the nucleus following the transcription of inflammation-related genes. However, it can be said that saffron exerts its anti-inflammatory properties by reducing the production of inflammatory proteins such as TNF-a, interleukin-1b (IL-1b), and IL-6 (22). Contrary to the generally favorable relationship between saffron supplementation and subclinical inflammation indices found in laboratory and animal studies, conflicting results have been reported from clinical trials, although some studies have reported a beneficial effect of saffron consumption on inflammatory cytokines. But others could not show a significant effect (23-26).

Therefore, while saffron supplementation seems to have beneficial effects in preventing the complications of diabetes, its role in factor with exercise training on some indicators of stress and inflammation is unclear. The present study aimed to investigate the interactive effect of 8 weeks of high-intensity intermittent training with saffron supplementation on cardiac stress markers and glycemic control in obese women with type 2 diabetes.

2. Methods

The present research design is quasi-experimental. The study population consisted of adult women aged 40 to 60 years, who after being summoned to the Diabetes Clinic and Medical Centers of Urmia, 35 people announced their presence. Criteria for inclusion in the present study include no history of regular exercise training, body mass index (BMI) of more than 30 kg /m^2, high body fasting blood sugar level above 130 mg/dl, no history of smoking, and no history of cardiovascular disease. After evaluating the inclusion criteria, 32 subjects were divided into 4 groups: 1. Saffron, 2. Saffron + HIIT, 3. Placebo, and 4. Placebo + HIIT.

In the initial evaluation session, the subjects were introduced to how to implement and apply the research interventions and then completed the questionnaires related to medical health and voluntary participation in the research. In the next session, pre-test anthropometric indices, including weight, height, body mass index (BMI), waist-to-hip ratio (WHR), and body fat percentage, also cardiac stress markers including IL-6, NT-proBNP, and GDF-15 were taken from the brachial vein blood sample (5 cc).

Saffron supplementation protocol

Subjects consumed a powder capsule containing 100 mg of saffron and starch daily under the interventions, supplement + HIIT training, placebo, and placebo + HIIT, respectively (27).

Measurement of maximum oxygen consumption (Vo2max) and training protocol.

Bruce running test was used to measure maximum oxygen consumption (VO2max). This test is consisting of 7 steps three-minute and starts at a speed of 1.7 km/h with a 10% slope on the treadmill. After 10 minutes of warm-up, subjects started the test. After voluntary fatigue (according to the pressure perception criterion), the test was stopped, and their heart rate was recorded at the point of exhaustion (28). The primary training protocol also included: 8 weeks, 3 sessions per week, 4 running bouts on a treadmill with an intensity of 85-95% of maximum heart rate (MHR), and 4 rest interval periods with an intensity of 50-60% (MHR) (29). 72 hours after the last training protocol session, anthropometric characteristics and blood serum indices (stress markers) were measured using the ELISA method. Blood samples were taken immediately to separate serum from blood plasma using a centrifuge for 15 minutes at a speed of 3 meters per minute.

Statistical Analysis

The statistical method of the present study was performed using descriptive statistics indicators, including mean and standard deviation in the form of tables and graphs using Excel software. The research findings were analyzed using a two-way analysis of variance (4 * 2) using SPSS software version 25 at the level ($P \leq 0.05$).

3. Results

Mean, and standard deviation of descriptive, anthropometric characteristics including age, height, weight, BMI, fasting glucose and insulin levels, and glycosylated hemoglobin (HbA1c) are shown in Table 1.

Table (1): Mean and standard deviation (M ± SD) of descriptive and anthropometric indices of the subjects

Groups	Saffron		Saffron + HIIT		Placebo		Placebo + HIIT	
Intervention times	pre- test	Post-test	pre- test	Post-test	pre- test	Post-test	pre- test	Post-test
Age (years)	47/48 ± 7/68		49/18 ± 7/34		47/36 ± 8/29		45/.05 ± 9/10	
Height (cm)	162 ± 8/84		161/12 ± 5/78		159/25 ± 6/53		160/35 ± 6/23	
Weight (kg)	80/88 ± 10/37	79/49 ± 11/74	82/10 ± 9/31	78/52 ± 8/43	81/37 ± 10/02	81/50 ± 8/55	80/13 ± 11/74	79/52 ± 9/39
BMI (Kg/m2)	30/35 ± 2/50	29/35 ± 2/45	32/23 ± 2/02	29/14 ± 1/69	32/71 ± 2/15	32/32 ± 2/60	31/78 ± 1/41	30/64 ± 1/18
Fasting blood Glucose (ml/dL)	165/25 ± 43/6	160/15 ± 39/19	167/68 ± 48/8	158/26 ± 61/24	165/09 ± 39/28	164/11 ± 40/06	160/21 ± 46/1	157/90 ± 42/25
Fasting Blood insulin (pmol/L)	160/34 ± 23/38	156/51 ± 18/36	155/51 ± 18/65	149/13 ± 19/41	161/28 ± 28/12	160/08 ± 26/19	153/59 ± 21/34	151/26 ± 20/78
HbA1c	7/54 ± 1/67	7/13 ± 1/04	7/31 ± 1/48	6/67 ± 1/08	7/23 ± 1/43	7/18 ± 1/18	6/89 ± 1/78	6/17 ± 1/27

The results of IL-6, NT-proBNP, and GDF-15 levels are shown in Table 2 and Figure 1, respectively.

Table (2): Mean and standard deviation of IL-6 and NT-proBNP levels among research groups

	Saffron		Saffron + HIIT		Placebo		Placebo + HIIT	
Variables	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test
IL-6 (pg/ml)	90.16 ± 15.04	89.37 ± 16.18	89.36 ± 13.08	86.50 ± 14.04 *	90.68 ± 14.11	90.13 ± 16.68	89.57 ± 15.28	88.31 ± 17.14
NT-proBNP (pg/ml)	651.34 ± 119.18	618.87 ± 121.23 *	648.35 ± 100.44	598.64 ± 115.29 * ¥	678.41 ± 100.12	669.16 ± 95.14	699.16 ± 106.13	686.73 ± 116.35 *

* Significance relative to pre-test time (P≤0.05). ¥ Significance relative to groups (P≤0.05).

+ HIIT groups in the post-test compared to pre-test (P ≤0.000) so that their levels are significantly reduced. However, this decrease was greater among the HIIT + Saffron group than in the other groups (P ≤0.001).

The results of the analysis of variance (4 × 2) test related to IL-6 and NT-proBNP variables in Table 2 show a significant difference between the levels of both components in the Saffron, Saffron + HIIT, and placebo

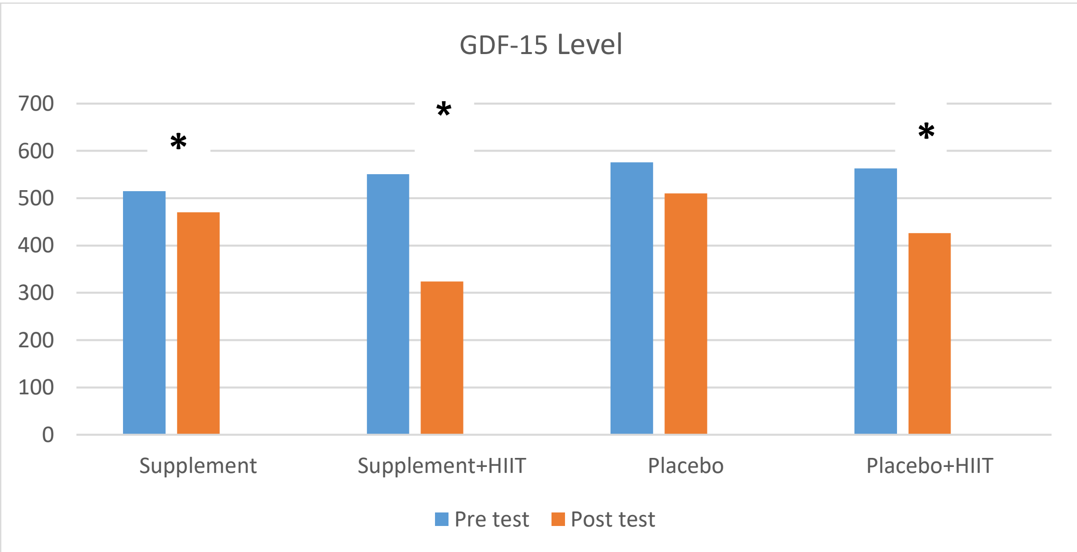

Figure (1): Changes in serum GDF-15 levels in the subjects of the present study
* Significance relative to pre-test time (P≤0.05). ¥ Significance relative to groups (P≤0.05).

According to the results (Figure 1) related to changes in GDF-15 levels, it can be said that GDF-15 levels in the Saffron, Saffron + HIIT, and placebo + HIIT groups in the post-test decreased significantly compared to the pre-test (P≤0.000). However, this decrease is more significant in the HIIT + Saffron group (P≤ 0.003).

4. Discussion

This study aimed to investigate the interactive effect of 8 weeks of HIIT training with saffron supplementation on stress and inflammatory indices in obese women

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with type 2 diabetes. The results showed that IL-6 and NT-proBNP levels in the Saffron, Saffron + HIIT, and placebo + HIIT groups were significantly reduced in the post-test compared to the pre-test (time effect). These results were consistent with the findings of Silva et al. (2022), Francois et al. (2015), Liu et al. (2019), and Delfan et al. (2020) (30-33). In previous studies, stress indicators in response to exercise have not been specifically studied. However, the study of critical cardiac markers in people with type 2 diabetes as one of the predictors of heart failure was shown that higher levels of IL-6, hs-CRP, hs- cTnT, and NT-proBNP were significantly associated with an increased risk or progression of heart failure in patients with type 2 diabetes (7). Type 2 diabetes is characterized by more insulin resistance in skeletal muscle and a lack of insulin secretion in the final stage. In general, T2DM increases blood glucose levels and components of the metabolic syndrome, including hypertension, triglycerides, decreased high-density lipoprotein levels, and abdominal obesity (34). Increased inflammatory factors including tumor necrosis factor (TNF-α), reactive protein C (CRP), and IL-6 due to increased abdominal obesity, different signals to regulate various factors including insulin sensitivity, stress Sends oxidative, energy metabolism, blood clotting and inflammatory responses (35). GDF-15 has recently been identified as an important plasma marker associated with cardiac metabolic syndrome. GDF-15 has been termed the macrophage inhibitor cytokine-1 (MIC-1) due to its inhibition of TNF production in lipopolysaccharide-stimulated macrophages(36). Recently, GDF-15 has been shown to reduce food intake, body weight, and obesity and improve glucose tolerance in typical, high-fat diets (37). In a previous study, it was found that acute exercise significantly increased serum GDF-15 levels in obese men, possibly improving glucose metabolism in them, whereas levels decreased significantly after a few hours(38). In the present study, it was also shown that eight weeks of high-intensity interval training along with saffron supplementation caused significant levels. However, it can be said that HIIT training along with saffron supplementation due to their anti-inflammatory properties reduce serum GDF-15 levels in obese women with type 2 diabetes, which these changes were associated with improved anthropometric indices such as Weight and BMI. Higher levels of GDF-15 and a known cardiovascular risk factor such as NT-proBNP have also been a predictor of cardiovascular mortality in patients with diabetic nephropathy (39). However, there are limited studies on the effect of exercise on GDF-15 and NT-proBNP marker levels. Ebadi et al. (2021) reported that eight weeks of HIIT training with astaxanthin supplementation significantly affected NT-proBNP levels and insulin resistance in diabetic rats (40). In another study, Galliera et al. (2014) showed that GDF-15 and NT-proBNP levels significantly increased in rugby players after strenuous exercise sessions (41). This study emphasized the role of two essential factors, GDF-15 and NTproBNP as markers for evaluating cardiovascular function in players. However, Munk et al. (2014) found that long-term exercise training did not affect GDF-15 and NT-proBNP levels (42), which was inconsistent with the present study results. One of the reasons for this discrepancy was probably the type of subjects, so they studied people with coronary artery disease, while in the present study, the subjects were obese women with type 2 diabetes.

The biologically active components of saffron have been reported to exert responses to inflammatory and anti-inflammatory agents through their effect on insulin resistance. According to previous reports, crocin, as an active ingredient in saffron, can inhibit the production of IL-6 and TNF-a, thereby activating anti-inflammatory signals in hyperglycemic conditions (43). In addition, it is suggested that the anti-inflammatory activity of saffron is due to its potent antioxidant properties and its radical inhibition. Saffron may suppress the increase in oxidative stress induced in type 2 diabetes and may begin by depleting reactive oxygen species, strengthening the antioxidant defense system, and regulating the immune response (44). In our study, supplementation of saffron as a 100 mg capsule per day for eight weeks reduced the inflammatory marker IL-6, which was observed in both the supplement group and the supplement group + HIIT training. However, these changes were more significant in the combined group (supplement + HIIT training), probably due to the anti-inflammatory properties of saffron and HIIT training. One of the mechanisms through which exercise training reduces the serum levels of inflammatory cytokines, including IL-6, is the reduction of fat mass and the expression of inflammatory mediators caused by that (45), in the present study, these changes were associated with a decrease in fat mass and BMI subjects.

Exercise volume and intensity as the basis of exercise training protocol is another important factor in controlling the risk of diabetes and its complications. Although low- or moderate-intensity continuous aerobic training is recommended for use in diabetics, high-intensity intermittent training (HIIT) has been reported to be more effective in rejuvenating the heart, controlling blood glucose, and many other clinical complications of diabetes (32). Although low- or moderate-intensity continuous aerobic training is recommended for use in diabetics, high-intensity intermittent training (HIIT) has been reported to be more effective in optimal heart function, blood glucose control, and many other clinical complications diabetes (32). Støa et al. (2017) found that the HIIT training program with an intensity of 85-95% of maximum heart rate significantly increased VO_{2peak} and decreased hemoglobin A1c (HbA1c), body wand eight in subjects with T2D (46). Karstoft et al. (2013) observed the effectiveness of HIIT in further improvements in VO_{2peak}, body weight, fat mass, and glycemic control compared with continuous training in the form of walking (47). Mitranun et al. (2014), also reported that HIIT improved cardiovascular risk factors, including HbA1c, glycemic control, and Vo2max, as well as other cardiovascular risk factors in T2D patients compared to traditional continuous training (48), which was consistent with the results of the present study.

In conclusion, the results of the present study showed that HIIT training and saffron supplementation (combination of both) possibly improved glucose metabolism through anti-inflammatory properties due to the reduction of levels of stress-inflammatory markers such as GDF-15, NT-proBNP, and IL-6 improving glucose metabolism and insulin resistance in obese women with type 2 diabetes.

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