



# The Effect of High-Intensity Interval Training on the Adiponectin and TNF- $\alpha$ Levels of Serum and Adipose Tissues in Rats Fed with a High-Fat Diet Plus Sucrose Solution

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## Abstract

**Background:** Adipocytokines secreted by adipose tissue are suggested to play a significant role in developing obesity-related complications. On the other hand, regular high-intensity interval training (HIIT) has been shown to reduce the risk of metabolic complications in obese subjects.

**Objectives:** The effect of HIIT was evaluated on serum and adipose tissues (inguinal and retroperitoneal) adiponectin and TNF- $\alpha$  levels in rats fed with a high-fat diet plus sucrose solution (HFDS).

**Methods:** Thirty-two male Wistar rats were randomly divided into HFDS and standard diet (SD) groups. After 12 weeks, each group was divided into a sedentary group and a HIIT group. An HIIT program was performed three times/week for eight weeks. Inguinal and retroperitoneal adipose tissues and serum were collected to assay adiponectin and TNF- $\alpha$  levels. Also, serum glucose and insulin levels, insulin resistance index (HOMA-IR) were measured.

**Results:** HFDS significantly increased weight gain, weight of inguinal ( $P = 0.001$ ) and retroperitoneal fat depots ( $P < 0.001$ ), and HOMA-IR ( $P < 0.001$ ) but reduced serum TNF- $\alpha$  levels ( $P = 0.011$ ). HIIT was able to decrease weight gain and fat mass ( $P < 0.05$ ) but did not affect inguinal and retroperitoneal fat depots' adipokines (adiponectin and TNF- $\alpha$ ) levels and HOMA-IR ( $P > 0.05$ ).

**Conclusions:** Treating rats on a standard diet with a training protocol was associated with weight loss, and decreased adipose tissue, and beneficial changes in adiponectin and TNF, suggesting that HIIT could prevent diseases associated with low-grade systemic inflammation.

**Keywords:** HIIT, High Fat Diet, Insulin Resistance, White Fat Depots, Adipokines

## 1. Introduction

To date, few studies have focused on combining a high-fat diet plus sucrose (HFDS) solution, which mimics the development of the Western diet (1). Consumption of HFDS solution is a known cause of insulin resistance and metabolic syndrome because it disrupts metabolic white adipose tissue (2). White adipose tissue (WAT) is now recognized as a highly active metabolic tissue and a vital endocrine organ, which is divided into two types: subcutaneous and visceral (3). The difference between subcutaneous and visceral adipose tissues is their specific regulation, fat storage, homeostasis, energy maintenance, and adipokine secretion (1, 3). Adipocytes secrete adipocytokines to regulate body weight and food ingestion, glucose homeostasis, coagulation, fibrinolysis, and inflammatory processes (4). Adipocytokines have pro/anti-

inflammatory properties that affect local and systemic inflammation (5, 6). In individuals with a normal metabolic state, there is a balance between pro/anti-inflammatory adipocytokines (4-6). Furthermore, obesity-induced anti-inflammatory and the down-regulation of a large number of protective molecules (such as adiponectin) and pro-inflammatory cytokines (such as Tumor necrosis factor- $\alpha$ ) are simultaneously upregulated (4, 7). Adiponectin (Acrp30) is a 30-Mr adipose tissue-derived factor. It is similar to exercising, increasing glucose uptake by skeletal muscle, and inhibiting liver gluconeogenesis (8). Also, it can stimulate fatty acid oxidation. Hence, it reduces the content of liver and tissue triglycerides in muscles (6, 9). TNF- $\alpha$  is an effective pro-inflammatory, immunomodulatory cytokine composed of activated macrophages, monocytes, CD<sup>4+</sup> lymphocytes, natural killer cells, neu-

trophils, mast cells, eosinophils, and neurons. It involves a variety of metabolic disorders such as T2DM and obesity (5, 6, 9). TNF- $\alpha$  blocks insulin action and causes insulin resistance, related to impaired glucose tolerance, increased insulin resistance, islet dysfunction, and increased risk of T2DM (5). The role of insulin is different in different metabolic tissues. Insulin resistance is generally associated with weight gain and white adipose tissue dysfunction (1, 5). In addition, several adipokines, such as adiponectin and TNF- $\alpha$ , are all associated with this disease (5, 6). Controlling metabolic syndrome and other comorbidities in the population is a challenge in modern society (1). High-intensity interval training (HIIT) combines short-term high-intensity exercise with long-term recovery (5, 10). Exercise and diet play a vital role in weight gain and weight loss, metabolism, and physiological function, (2, 5, 10). However, very few studies have dealt with HIIT and diet combination when trying to identify the dependent effects of exercise and diet on pro/anti-inflammation.

## 2. Objectives

Based on the pathophysiological dysfunction caused by obesity and the differences in the secretion of adipokines between subcutaneous and visceral fat deposits, on the one hand, and the effect of physical exercise on the quality of reducing fat deposits, on the other, this study aimed to evaluate inguinal fat deposits (as subcutaneous fat), retroperitoneal (as visceral fat) reactions, serum levels of adiponectin, TNF- $\alpha$ , HOMA-IR, and compositional parameters in rats withstanding HFDS or HIIT.

## 3. Methods

### 3.1. Animal Care

Animals were treated under animal care guidelines and ethical procedures approved by the Mazandaran University Ethics Committee. Thirty-two male Wistar rats (4 - 6 weeks old) were purchased from the Pasteur Institute in Tehran. The rats were kept in cages (four rats per cage) and maintained in a controlled light/dark cycle (12/12 hours) at  $22 \pm 2^\circ\text{C}$ . After adapting to their living conditions for a week, the animals were divided equally into standard diet (SD) and high-fat diet plus sucrose solution (HFDS) groups (phase 1). In the first phase (12 weeks), the rats had free access to HDfS and SD. The standard diet was purchased from the Behparvar Co., Iran. HFDS consisted of a standard diet in a separate container + 12% oil mixture + 30% (w/v) aqueous sucrose solution (11, 12). The mixed oil used for cooking and salad was purchased from the Iranian Margarine

Company. After 12 weeks of HFDS or SD, each group was assigned as either a sedentary (S) group or a training (T) group (phase 2; three times/week, eight weeks).

### 3.2. Training Protocol

In the second phase, the rats became familiar with running on the treadmill for one week (three times/week, 10 minutes/session). The main HIIT training program consisted of a 3-minute running course (40 m/min) and a 3-minute active recovery course (20 m/min). Each session was repeated six times per session (total time: 36 min) with  $15^\circ$  incline on a motorized treadmill. The duration, speed, and slope gradually increased up to 36 minutes, 40 m/min, and  $15^\circ$ , respectively, over six weeks. Each training session included 10 minutes of warm-up and relaxation (10 m/min, 0% slope). This training program was adopted from a previous animal study (13), where a speed of 40 m/min and a slope of  $15^\circ$  caused approximately  $\geq 85\%$   $\text{VO}_{2\text{Peak}}$ . Rats in the sedentary group did not perform any activity and only stood on a treadmill for the same exercise time as the training group. In the second phase, the rats were allowed to eat HFDS or SD freely.

### 3.3. Sample Collection

After 20 weeks of treatment, 72 hours following the last training, the rats were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (3 - 5 mg/kg) under fasting conditions. Then, 5 mL of blood was drawn from the abdominal vena cava and centrifuged (3000 rpm;  $4^\circ\text{C}$ ; 15 minutes). The separated serum was immediately frozen and stored at  $-20^\circ\text{C}$  for further analysis. The inguinal (depots as subcutaneous WAT) and retroperitoneal (depots as visceral WAT) fat depots were collected and weighed.

### 3.4. Blood and tissue measurements

Serum glucose was measured by enzyme colorimetry (Pars Azmoun, Tehran, Iran). The ELISA kit was used to measure the concentration of serum insulin, adiponectin, and TNF- $\alpha$  (Hangzhou Dongfang Biopharmaceutical Co., Ltd., China). To calculate HOMA-IR levels, we used the formula for the HOMA-IR score as follows (14):

$$\text{HOMA} - \text{IR} = \frac{\text{insulin} \left( \frac{\text{mIU}}{\text{L}} \right) \times \text{blood sugar} \left( \frac{\text{mmol}}{\text{L}} \right)}{22.5}$$

Also, 100 mg of inguinal and retroperitoneal fat was used for homogenization to measure the concentration of adiponectin and TNF- $\alpha$  in tissues.

### 3.5. Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normality of the data for all variables. A two-way analysis of variance was used to determine the main effects of diet (SD and HFDS), training status (sedentary and training), and their interactions on serum and adipose tissue variables. The statistically significant difference was considered to be at a 0.05 level. Also, SPSS software, version 16.0, was used for data analysis.

## 4. Results

Table 1 shows the body weight of the animals for 20 weeks and changes in adipose tissue. HFDS significantly increased the weight of both inguinal ( $P = 0.001$ ) and retroperitoneal ( $P = 0.000$ ) fat depots compared to the SD group. Eight weeks of HIIT with SD significantly reduced the weight of the inguinal ( $P = 0.030$ ) and retroperitoneal ( $P = 0.018$ ) fat depots. HFDS significantly increased the relative weight of the inguinal ( $P = 0.000$ ) and retroperitoneal ( $P = 0.000$ ) fat depots. Compared to the HFDS training group, the relative weight of retroperitoneal fat in the SD training group was significantly reduced ( $P = 0.040$ ).

HFDS significantly increased serum glucose levels ( $P < 0.001$ ) and HOMA-IR ( $P < 0.001$ ) compared to SD (Table 2). HIIT did not significantly affect the serum glucose concentrations and HOMA-IR. It only decreased serum insulin concentrations compared to the sedentary group in the SD regimen ( $P = 0.001$ ).

Table 2 shows changes in serum adipokines and adipose tissue levels during the 20-week treatment period. Statistically significant diet-training interaction effects were found for serum adiponectin levels ( $P = 0.024$ ). Diet affected serum TNF- $\alpha$  levels so that the serum TNF- $\alpha$  levels of the SD training group were significantly higher than those of the HFDS training group ( $P = 0.011$ ). The inguinal fat diet-training interaction was statistically significant ( $P = 0.019$ ), but no effect was found for TNF- $\alpha$  levels on the retroperitoneal fat depots ( $P = 0.928$ ). Furthermore, a simple main effect analysis showed no significant differences in the inguinal and retroperitoneal TNF- $\alpha$  levels between diet and training ( $P > 0.05$ ).

## 5. Discussion

This study evaluated the response of different white fat depots and circulating levels of adiponectin and TNF- $\alpha$  in rats receiving HFDS and HIIT. We hypothesize that HIIT can cause positive metabolic changes in adipose tissue by affecting the quality of adipose tissue and, therefore, anti-inflammatory and pro-inflammatory markers secreted by

adipokines. HIIT can also significantly affect the weight of retroperitoneal and inguinal fat depots. Still, it has no significant effect on the production of adiponectin and TNF- $\alpha$ , body weight, and HOMA-IR.

Regarding adiponectin and TNF- $\alpha$ , it was observed in this study that regardless of the type of diet, training could not promote their changes in all groups. HFDS applied in this study did not affect circulating (serum), retroperitoneal, and inguinal adiponectin concentrations. However, serum levels of TNF- $\alpha$  showed a significantly lower value in HFDS. Contrary to some previous studies, the results of this study did not confirm that adiponectin is an anti-inflammatory marker. Since HIIT significantly reduced the impact of fat depots, we expected HIIT to alter the circulating concentrations of adipose tissue and anti-inflammatory and pro-inflammatory markers. Interestingly, regardless of the type of diet, HIIT did not affect adiponectin and TNF- $\alpha$  on the inguinal and retroperitoneal levels.

Even though diet caused this mild inflammatory activation (7), it is worth noting that HIIT reduced adiponectin levels in obese animals (7, 15). It is well known that the stress promoted by physical exercise is related to increased catecholamine emissions. The catecholamine receptors in macrophages are critical in regulating the inflammatory response (16). In obesity, a high-fat diet will increase catecholamines, and catecholamines will inhibit adiponectin expression through cAMP response element-binding proteins (16-18). HFDS proposed in our study did not significantly increase the body weight of the rats. Therefore, it can be stated that obesity has not been correctly induced, which may be the reason for the lack of significant changes in the values of circulating adiponectin and fat deposition. As previously shown, adiponectin and TNF- $\alpha$  are associated with obesity and related diseases such as metabolic syndrome (7, 19-21). This suggests that the impact of training on inflammatory factors may depend on the redistribution of body composition rather than on absolute weight loss. Some studies also reported that these factors did not fluctuate during physical training (20-22). Physical activity can reduce circulating levels of IL6 and TNF- $\alpha$  by affecting the significant reduction of adipose tissue and visceral fat and inhibiting the presentation of pro-inflammatory cytokine genes (23-26). Cytokines are produced mainly by infiltration of monocytes and macrophages into adipose tissue. However, other immune cells, such as lymphocytes and natural killer cells, can also produce it. High levels of TNF- $\alpha$  in adipose tissue are associated with cell death, which is caused by inflammation and acute-phase proteins by macrophages at the tissue site (27, 28). Also, cytokines activate some intracellular kinases that inhibit insulin signaling and prevent glucose uptake (7).

**Table 1.** Changes in the Adipose Tissues and Body Weight Over 20 Weeks of Diet and Training<sup>a</sup>

Variables	SD		HFDS		Two-Way ANOVA P Values		
	Sedentary	Training	Sedentary	Training	Diet	Training	Interaction
Final body weight (g)	427.7 ± 54.45	386.2 ± 38.68	440.4 ± 56.87	408.1 ± 39.27			
Weight changes (g)	235.2 ± 44.56	230.6 ± 32.96	259.4 ± 61.33	248.3 ± 40.18	0.084	0.096	0.460
Inguinal fat (g)	5.079 ± 1.177	4.431 ± 1.084	8.108 ± 2.482	6.047 ± 1.601	0.001	0.030	0.242
Retroperitoneal fat (g)	5.241 ± 0.898	3.069 ± 0.397	9.410 ± 4.163	7.302 ± 2.721	0.000	0.018	0.961
Ingu fat/body (%)	0.012 ± 0.003	0.011 ± 0.002	0.018 ± 0.003	0.014 ± 0.004	0.000	0.117	0.277
Retro fat/body (%)	0.012 ± 0.001	0.008 ± 0.001	0.021 ± 0.006	0.018 ± 0.007	0.000	0.040	0.732

<sup>z</sup> Abbreviations: SD, standard diet; HFS, high-fat diet plus sucrose solution; Ingu, Inguinal fat; Retro, retroperitoneal fat.

<sup>a</sup> The values are expressed as mean ± SD (n = 8 rats per group).

**Table 2.** Adipokine Levels and Metabolic Parameters of Serum and Adipose Tissues at the End of the Experiment<sup>a</sup>

Variables	SD		HFDS		Two-Way ANOVA P Values		
	Sedentary	Training	Sedentary	Training	Diet	Training	Interaction
Glucose (mmol/L)	5.86 ± 0.638	5.66 ± 0.579	8.31 ± 0.643	7.86 ± 1.060	0.000	0.253	0.661
Insulin (mIU/L)	5.10 ± 0.32	3.99 ± 0.30	5.99 ± 0.79	5.25 ± 0.63	0.016	0.028	0.001
HOMA-IR	1.36 ± 0.209	1.00 ± 0.147	1.84 ± 0.303	1.85 ± 0.399	0.000	0.108	0.093
TNF-α (mg/L)	176.7 ± 29.33	202.24 ± 29.22	151.80 ± 31.60	167.01 ± 26.64	0.011	0.073	0.639
Ingu TNF-α (pg/mg)	1.22 ± 0.093	1.31 ± 0.069	1.33 ± 0.069	1.28 ± 0.074	0.212	0.472	0.019
Retro TNF-α (pg/mg)	1.13 ± 0.075	1.19 ± 0.092	1.12 ± 0.107	1.16 ± 0.116	0.620	0.182	0.928
Adiponectin (mg/L)	10.71 ± 0.711	9.87 ± 1.356	9.22 ± 0.802	10.44 ± 1.467	0.293	0.658	0.024
Ingu Adiponectin (pg/mg)	0.063 ± 0.004	0.063 ± 0.003	0.062 ± 0.004	0.059 ± 0.009	0.263	0.562	0.646
Retro Adiponectin (pg/mg)	0.058 ± 0.004	0.059 ± 0.008	0.059 ± 0.006	0.064 ± 0.008	0.200	0.280	0.533

<sup>z</sup> Abbreviations: SD, standard diet; HFDS, high-fat diet plus sucrose solution; Ingu, inguinal fat; Retro, retroperitoneal fat.

<sup>a</sup> The values are expressed as mean ± SD (n = 8 rats per group).

Monocyte-derived and circulating TNF-α is a recognized cytokine that induces insulin resistance and generally responds to lifestyle interventions (29). Previous studies have shown that patients with metabolic syndrome have significantly lower serum TNF-α levels after 12 weeks of HIIT (30, 31). Research reported that after 24 weeks of HIIT in obese mature people, serum levels of IL6 and TNF-α were significantly reduced (26). HIIT is also independent of fat cell size, macrophage accumulation in adipose tissue, adipose tissue inflammation, or adipose tissue markers that increase adipose tissue insulin sensitivity (32). The meta-analysis by Jelleyman et al. shows that HIIT is more effective in improving insulin resistance than non-exercise and continuous exercise. Notably, the most significant impact was on patients with type 2 diabetes or metabolic syndrome (21). According to reports, HIIT can improve insulin sensitivity in metabolic disorders. Mechanisms, including increased GLUT4 content, increased aerobic enzyme capacity, and mitochondrial biogenesis, have been proposed to improve insulin resistance (33). There are conflicting re-

sults on the improvement of insulin resistance by HIIT; some report no change in HOMA-IR, while others report a 20% improvement in HOMA-IR (33). Our result shows that HIIT does not affect the HOMA-IR progress. Our HIIT program did not change fasting blood glucose levels but significantly reduced fasting serum insulin levels (Table 2). According to a review study, HIIT has usually a small effect on lowering blood glucose levels (either long HIIT or short HIIT) but does not affect fasting insulin (33). HIIT appears to have a small but significant effect on insulin resistance. Other studies have reported that despite weight loss after exercise, no changes have been observed in circulating adiponectin levels (34, 35). One possible explanation for this finding is that adiponectin increases due to the stimulation of mitochondria in fat cells after physical activity. Mitochondrial function in adipocytes plays an essential role in synthesizing adiponectin and TNF-α; on the other hand, mitochondrial dysfunction in adipocytes reduces adiponectin synthesis. This process will be reversed as mitochondrial production increases (36, 37).

The HIIT intensity can be considered a significant reason for the differences observed in the studies. Given this, according to the conclusions of a recent systematic review study, specified HIIT procedures at an intensity close to the maximum and higher can only have a significant impact on the discharge. Therefore, intensity must be controlled by precise techniques such as lactic acid concentration and respiratory exchange ratio (10). Before conclusions can be drawn, more research is needed to determine the effects of diet- and/or exercise-induced weight loss on pro/anti-inflammatory effects.

### 5.1. Conclusion

In summary, our research shows that HIIT does not affect the levels of circulating and white fat depots' adipokines (adiponectin and TNF- $\alpha$ ) in HFDS-fed rats. However, the HIIT program can significantly reduce fat depot weight in this animal model.

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### Footnotes

**Authors' Contribution:** Ali Delpisheh developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and is a guarantor. Alireza Safarzade contributed to the development of the protocol, abstracted data, and prepared the manuscript.

**Conflict of Interests:** The authors have no conflicts of interest.

**Data Reproducibility:** It was not declared by the authors.

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