High-Intensity Interval Training Versus Moderate Intensity Combined Training (Resistance and Aerobic) for Improving Insulin-Related Adipokines in Type 2 Diabetic Women

Ebrahim Banitalebi¹, Mohammad Faramarzi¹, * and Samira Nasiri¹

¹Department of Sport Sciences, Shahrekord University, Shahrekord, Iran

*Corresponding author: Department of Sport Sciences, Shahrekord University, Shahrekord, Iran. Email: md.faramarzi@gmail.com

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Abstract

Background: The impaired adipocytes secrete factors observed in diabetes contribute to insulin resistance. The purpose of the present study was to compare the effects of high-intensity interval versus moderate intensity combined resistance and aerobic training on some adipokines related to insulin resistance (interleukin-6 [IL-6], apelin, and monocyte chemoattractant protein 1 [MCP-1]) in women with type 2 diabetes.

Methods: Fifty two females with type 2 diabetes (aged 45 - 60 years, the HbA1C value of 6.5% or above, and fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L)) were assessed for eligibility. The participants were assigned to a HIIT group (n = 17), a combined resistance and aerobic training group (n = 17), and a control group (n = 18) randomly. The exercises included 10 weeks of combined training and HIIT.

Results: TNF-α concentrations changed significantly in the HIIT (P = 0.001) and combined training (P = 0.015) groups. The same test revealed that the differences were significant for the IL-6 in the HIIT (P < 0.000) and combined training (P < 0.000) groups. Data also showed significant differences in MCP-1 and IL-6 levels in the HIIT and combined resistance and aerobic training groups (P < 0.05). In addition, there were no significant changes in apelin in both groups after 10 weeks (P > 0.05). The ANCOVA test showed no significant differences in apelin (F = 0.511, P = 0.12).

Conclusions: The results highlight that exercise training, independent of the mode of training, is an effective strategy to improve some adipokines related to insulin resistance in women with type 2 diabetes.

Keywords: HIIT, Combined Training, Adipocytokine, Diabetes

1. Background

Physical activity/exercise is a well-established therapeutic tool to protect against type 2 diabetes (1). Adipose tissue, particularly visceral adipose tissue, expresses, synthesizes, and releases a variety of metabolically active molecules, called adipokocytes such as leptin, tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), interleukin-6 (IL-6), chemerin, omentin, vispin, visfatin, and apelin (2, 3) that act in an autocrine, paracrine, and endocrine manner to regulate metabolic and inflammatory biological processes (4) in some metabolic syndromes (5). It has been shown that adipokine dysfunction is one of the leading mechanisms associated with type 2 diabetes (6). However, the effect of exercise training on diabetes type 2-induced dysregulated adipokocytes depends on the type, intensity, and duration of exercise training. Hence, it is difficult to compare the findings reported by previous studies (7). There is an increasing evidence that glycemic control is improved by intensities above recommended prescription in type 2 diabetic individuals (8). We hypothesized that these combined and high-intensity interval training would exert beneficial effects for diabetic patients.

2. Objectives

The purpose of this study was to examine the effects of high-intensity interval vs. moderate intensity combined resistance and aerobic training on some adipokines related to insulin resistance (interleukin-6 [IL-6], apelin, and MCP-1) in type 2 diabetic women.

3. Methods

This study was a single-blind randomized clinical trial conducted in Shahrekord University (2016)
Based on the CONSORT statement (9). The protocol was registered in the Iranian Clinical Trial Registry, IRCT: IRCT2014111801999N10. The Ethics Committee of Shahrekord University (code No.: SKU94/210) granted the ethical approval of the study. Participants were recruited from patients registered in Shahrekord Diabetes Association (Shahrekord, Iran) according to the following inclusion criteria: Diagnosed with T2D by a physician based on the American Diabetes Association criteria (HbA1C ≥ 6.5%, fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L)) (10), being sedentary (defined as having no more than 20 min exercise per week over the past six months) (11), being a 45 - 60-year-old pre-menopausal woman with a body mass index (BMI) between 25 and 35 kg/m², having no diagnosed type 1 diabetes, and having lost or gained no more than 5 kg in weight during the previous six months. The participants were excluded if they had blood pressure ≥ 160/100 mmHg, fasting triglyceride ≥ 500 mg/dL, serious cardiovascular or musculoskeletal problems, thyroid disorder, cancer, hormonal disorder, kidney and liver diseases, and history of surgery or if they were smokers or used drugs or alcohol. We concluded that a sample size between 10 and 20 could provide the statistical power of 80% into the effect of HIIT versus combined training clinically and detect the potential difference in the means of 2% after a 10-week training. The power and sample size calculation of this study determined 17 subjects per group based on a predicted expected dropout rate of 20%. Every participant provided written informed consent.

Of 150 recruitments, only 54 subjects met the inclusion criteria (Figure 1). Eligible subjects were explained about the study protocol and informed about the risks and benefits of this study, both verbally and in writing. They were assured that all answers would be kept strictly confidential.

Concealed randomization in the variable blocks of six was conducted by a research assistant not involved in the research by using a computer-generated random number sequence. The participants were stratified according to the HbA1c level. Sequential treatment allocations were enclosed in numbered, opaque, sealed envelopes, and distributed by the same research assistant to the groups after the baseline assessment. The participants were randomly assigned to the HIIT group (n = 17), the A + R group (n = 17), or the control group (n = 18) (Figure 1).
the ELISA technique using a microplate reader. HOMA-IR was calculated by computing the following equation (16):

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\text{Fasting glycermia (mmol/L) \times Fasting insulin (mIU/L)} / 22.5
\]

Participants who used insulin injection were excluded for the HOMA-IR analysis. Interleukine-6 [IL-6], apelin, and MCP-1 levels were measured by using commercial Elisa kits (Table 3).

3.5. Statistical Analyses

All values are represented as means ± SD. For testing the normality of distribution, the Kolmogorov-Smirnov test was used. Data were analyzed by a Dependent t-test to
Table 1. The Comparison of Changes in Adipokine Related to Insulin Resistance Before and After 10 Weeks of Exercise Interventions

| Variables | Pretest | Posttest | P Value Within Group | F | P Value Between Groups |
|-----------|---------|----------|----------------------|---|-----------------------|
| Apelin (pg/mL) |         |          |                      |   |                       |
| HIIT      | 256.65 ± 25.12 | 279.12 ± 50.08 | 0.13 | 0.511 | 0.12 |
| Combined training | 286.56 ± 42.12 | 266.26 ± 56.00 | 0.09 |          |          |
| Control   | 302.44 ± 38.03 | 312.23 ± 63.03 | 0.712 |        |          |
| MCP-1 (pg/mL) |         |          |                      |   |                       |
| HIIT      | 260.14 ± 20.14 | 190.26 ± 15.12 | 0.001 | 5.011 | 0.009b |
| Combined training | 251.20 ± 32.12 | 212.74 ± 19.95 | 0.045 |          |          |
| Control   | 263.78 ± 32.12 | 266.11 ± 12.20 | 0.732 |        |          |
| IL-6 (pg/mL) |         |          |                      |   |                       |
| HIIT      | 1.89 ± 0.95 | 1.21 ± 1.11 | 0.009 | 5.511 | 0.008b |
| Combined training | 2.03 ± 1.08 | 1.50 ± 1.32 | 0.019 |          |          |
| Control   | 2.12 ± 1.24 | 1.88 ± 2.01 | 0.261 |        |          |

Abbreviations: Combined training, resistance and aerobic training; control group, subjects not participating in exercise training; HIIT, high-intensity interval training; MCP-1, monocyte chemoattractant protein-1.
a Values are expressed as mean ± SD.
b Significant difference P < 0.01.
c Significant difference between P < 0.05.

Table 2. The Comparison of Changes in the Anthropometric Variables Before and After 10 Weeks of Exercise Interventions

| Variables | Pretest | Posttest | P Value Within Group | P Value Between Groups |
|-----------|---------|----------|----------------------|-----------------------|
| Body mass (kg) |         |          |                      |                       |
| HIIT      | 73.06 ± 21.62 | 77.00 ± 12.34 | 0.005 | 0.017b |
| Combined training | 76.30 ± 9.58 | 75.55 ± 9.23 | 0.004 |          |
| Control   | 71.44 ± 13.20 | 71.26 ± 13.06 | 0.000 |        |
| BMI (kg/m²) |         |          |                      |                       |
| HIIT      | 29.57 ± 2.77 | 28.97 ± 3.39 | 0.005 | 0.023b |
| Combined training | 30.57 ± 2.97 | 31.58 ± 8.61 | 0.004 |          |
| Control   | 30.70 ± 4.17 | 29.13 ± 4.41 | 0.42  |        |
| Body fat (%) |         |          |                      |                       |
| HIIT      | 42.64 ± 2.23 | 41.34 ± 4.34 | 0.000 | 0.000c |
| Combined training | 31.32 ± 4.63 | 27.99 ± 2.36 | 0.000 |          |
| Control   | 43.92 ± 2.49 | 42.64 ± 4.95 | 0.08  |        |
| WHR       |         |          |                      |                       |
| HIIT      | 1.01 ± 0.13 | 0.93 ± 0.06 | 0.000 | 0.006c |
| Combined training | 1.01 ± 0.25 | 0.97 ± 0.07 | 0.008 |          |
| Control   | 1.01 ± 0.018 | 0.98 ± 0.07 | 0.22  |        |

Abbreviations: BMI, body mass index; combined training, resistance and aerobic training; control group, subjects not participating in exercise training; HIIT, high-intensity interval training; WHR: circumference waist to hip ratio.
a Values are expressed as mean ± SD.
b Significant difference between two groups (P < 0.05).
c Significant difference between two groups (P < 0.01).

Compare pretest and posttest results in each group. An ANCOVA test was used to compare the changes in the experimental and control training groups after 10 weeks. When a significant F value was achieved, the Fisher’s Least Significant Difference (LSD) test was used to find the differences between various groups.

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Table 3. The Comparison of Changes in Some Serum Variables Before and After 10 Weeks of Exercise Interventions
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| Variables                 | Pretest          | Posttest         | P Value Within Group | F     | P Value Between Groups |
|---------------------------|------------------|------------------|----------------------|-------|------------------------|
| FFA (µmol/L)              |                  |                  |                      | 0.813 | 0.451                  |
| HIIT                      | 550.56 ± 90.56   | 542.52 ± 86.48   | 0.12                 |       |                        |
| Combined training         | 600.71 ± 73.52   | 599.50 ± 80.14   | 0.09                 |       |                        |
| Control                   | 555.14 ± 86.19   | 539.54 ± 89.11   | 0.231                |       |                        |
| FBG (mg/dL)               |                  |                  |                      | 1.853 | 0.171                  |
| HIIT                      | 210.07 ± 32.90   | 147.92 ± 41.17   | 0.000^b              | 3.622 | 0.036^c                |
| Combined training         | 216.00 ± 61.08   | 163.85 ± 71.47   | 0.062                |       |                        |
| Control                   | 177.28 ± 47.09   | 183.28 ± 60.70   | 0.690                |       |                        |
| Serum insulin (µU/ml)     |                  |                  |                      |       |                        |
| HIIT                      | 7.72 ± 2.63      | 4.97 ± 1.93      | 0.000^b              | 3.622 | 0.036^c                |
| Combined training         | 9.10 ± 2.62      | 5.93 ± 2.24      | 0.000^b              |       |                        |
| Control                   | 6.57 ± 2.06      | 6.21 ± 2.06      | 0.08                 |       |                        |
| HOMA-IR                   |                  |                  |                      | 5.511 | 0.009^b                |
| HIIT                      | 98.33 ± 3.08     | 93.44 ± 3.03     | 0.000^b              | 3.622 | 0.036^c                |
| Combined training         | 95.40 ± 3.08     | 92.50 ± 3.18     | 0.000^b              |       |                        |
| Control                   | 97.44 ± 4.36     | 97.00 ± 4.53     | 0.732                |       |                        |

Abbreviations: Combined training, resistance and aerobic training; control group, subjects not participating in exercise training; FBG, fasting blood glucose, HIIT: high-intensity interval training; HOMA-IR, homeostasis model assessment.

4. Results

Data from 10 participants who did not take part in the post-test assessment were excluded. Thus, only the available data of 42 participants with the mean age of 55.07 ± 5.92 years (dropout of 19.2%) who had completed the pre and post assessment was analyzed. The participants flow through the study can be found in the CONSORT flowchart in Figure 1. Subjects were being treated with oral hypoglycemic medications, 20 with insulin injections, and five with the combination therapy of insulin injection and oral drugs. The baseline characteristics are represented in Table 1. One-way ANOVA showed that there were no significant differences in terms of baseline characteristics between the groups, except for FBS (P = 0.021) and HbA1c (P = 0.005).

4.1. Adverse Events

No clinically severe adverse events were identified and reported during the 10-week intervention. However, most patients reported muscle soreness in the legs during HIIT (76%) and A+ R training (82%). The results were based on 14 participants in the control, 14 in HIIT, and 14 in combined training groups.

The effects of the 10-week combined resistance/endurance training and HIIT program on serum adipokine concentrations of diabetic female patients are shown in Table 1.

The data revealed that after 10 weeks of exercise training, there were significant changes in the fasting blood glucose in the HIIT group (P < 0.000). Paired t-test conducted on the data from experimental groups showed that the serum insulin levels showed significant increases in the HIIT (P < 0.000) and combined training (P < 0.000) groups following exercise training.

When comparing within-group changes, the HIIT and combined training groups had significantly lower MCP-1 levels at week 10 compared to baseline (P = 0.001 and P = 0.015, respectively). In the HIIT and combined training groups, changes in IL-6 were significantly lower compared to baseline at week 10 (P = 0.009 and P = 0.019, respectively) and MCP-1 in the combined training (P = 0.045) and HIIT (P = 0.001) groups at week 10 (P = 0.015). Changes in apelin were not significantly different within HIIT and combined training groups (P = 0.13 and P = 0.09, respectively). Furthermore, the ANCOVA test showed that there were no significant differences in fasting blood glucose concentrations (F = 1.853, P = 0.171) and apelin (F = 0.511, P = 0.12). Nevertheless, the ANCOVA test showed that significant differences were seen between groups in MCP-1 (F = 5.011, P = 0.009), IL-6 (F = 5.511, P = 0.008), insulin (F = 3.622,
peroxisome-proliferator-activated receptor concentrations may lay in its ability to activate the (27).

be explained by the lowering of serum adipokine levels abdominal subcutaneous adipose tissue reduction could training. It is probable that HIIT and combined-induced cur via different mechanisms from aerobic and resistance adipokine levels after HIIT and combined training oc- 

It seems patients with type 2 diabetes respond quite differently to HIIT and combined training. The mechanisms for the improvement in adipokine observed after HIIT and combined training in the current study are unclear. It has been suggested that the improved serum adipokine levels after HIIT and combined training occur via different mechanisms from aerobic and resistance training. It is probable that HIIT and combined-induced abdominal subcutaneous adipose tissue reduction could be explained by the lowering of serum adipokine levels (27).

The mechanism by which HIIT improves adipokine concentrations may lay in its ability to activate the peroxisome-proliferator-activated receptor γ coactivator (PGC-1α). Studies suggested that exercise intensity is the key factor influencing PGC-1α activation (28). It seems PGC-1α signaling is affected by every major signaling pathway that is activated in a contracting muscle fiber via myokines (29). A previous study showed that PGC-1 expression was greater in skeletal muscle fiber type Ila than in type I/Ilx fiber (30). Furthermore, several studies illustrated shifts of type I and Ilx fibers to type Ila fibers after HIIT (31).

Taken together, the results of the present study support the importance of high-intensity training and combined training program to improve type 2 diabetes and adipokines related to insulin resistance, despite the fact that some studies showed that combined training (aero- bic and resistance) and HIIT interventions could improve glucose homeostasis in overweight women with type 2 diabetes. The results highlighted that exercise training, independent of the mode of training (HIIT vs. combined training), is an effective training method to improve body composition, glycemic control, and adipokines related to insulin resistance in overweight individuals with type 2 diabetes.

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Footnote

Authors’ Contribution: Ebrahim Banitalebi and Mohammad Faramarzi designed the study. Samira Nasiri and Ebrahim Banitalebi supervised exercise training protocols. Ebrahim Banitalebi and Mohammad Faramarzi supervised laboratory exams and data collection. Ebrahim Banitalebi and Mohammad Faramarzi analyzed and interpreted the data. Ebrahim Banitalebi, Mohammad Faramarzi and Samira Nasiri wrote the first draft of the manuscript. Mohammad Faramarzi edited the paper. All authors contributed to the writing of the paper. All authors read and approved the final manuscript.

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