

The effect of a period of intense functional training on IL-10, Dectin-1, and IL-1Ra in prediabetic obese women

Running title: The effect of a period of intense functional training on some markers of M2 macrophages

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Abstract

Background: Obesity and prediabetes are associated with chronic low-grade inflammation, and macrophage-related markers such as IL-10, Dectin-1, and IL-1Ra play a key role in modulating inflammatory responses. The purpose of this study was to investigate the effect of a period of high-intensity functional training (HIFT) on IL-10, Dectin-1, and IL-1Ra in prediabetic obese women to assess the impact of this exercise modality on M2 macrophage markers.

Methods: Thirty eligible female volunteers aged 35–40 years were selected and homogenously divided into two groups: 1) control (n=15) and 2) training (n=15). The training group underwent a 16-week HIFT program based on CrossFit protocols, incorporating squats, deadlifts, barbell/dumbbell exercises, kettlebell swings, and aerobic/weight-bearing movements in a WOD (workout of the day) format (60 min/session). The control group maintained their daily routines without structured exercise. Serum levels of Dectin-1, IL-10, and IL-1Ra were measured via ELISA. Descriptive statistics (mean, standard deviation) were used for data analysis.

Results: After 16 weeks, HIFT significantly reduced Dectin-1 ($P=0.048$) and increased IL-10 ($P<0.0001$) and IL-1Ra ($P<0.0001$) levels in prediabetic obese women.

Conclusion: These findings suggest that 16 weeks of HIFT may enhance anti-inflammatory markers (IL-10, IL-1Ra) and modulate Dectin-1, potentially mitigating obesity-related inflammatory complications in prediabetic women.

Keywords: High-intensity functional training, Macrophages, Obesity, Prediabetes, Inflammation

Introduction

More than 650 million adults worldwide are obese. Obesity is often associated with several diseases such as cardiovascular disease and type 2 diabetes. In obesity, the accumulation of macrophages in white adipose tissue is often associated with insulin resistance. The increase in white adipose tissue associated with obesity often leads to the accumulation of immune cells, including macrophages, which contribute to low-grade chronic inflammation. Macrophages stimulate various responses in white adipose tissue. The classification of macrophages is based on their pro-inflammatory or anti-inflammatory roles. Adipose tissue macrophages can be divided into two main phenotypes: classical M1 macrophages and activated M2 macrophages. It is believed that M1 macrophages are more pro-inflammatory and secrete pro-inflammatory cytokines that ultimately inhibit proper insulin signaling in adipocytes. On the contrary, M2 macrophages are believed to be more anti-inflammatory and secrete anti-inflammatory cytokines that maintain functional insulin signaling (1). Obesity and insulin resistance have a close association with chronic inflammation in adipose tissue, where macrophages play a crucial role. M1 macrophages produce pro-inflammatory cytokines (TNF- α , interleukin IL-6, and MCP-1) and thus contribute to insulin resistance. In contrast, M2 macrophages play a role in maintaining tissue homeostasis and are prevalent in normal adipose tissue (2). Adipose tissue macrophages express characteristic genes of the anti-inflammatory M2 phenotype or "alternatively activated" macrophages in lean mice, such as Ym-1 protein, Arginase-1, and IL-10. In contrast, an increase in TNF α and iNOS expression was observed in obese mice, which is a characteristic of M1 or "classically activated" macrophages (3). In cases of obesity, adipose tissue macrophages shift from the M2 (anti-inflammatory) phenotype to the M1 (pro-inflammatory) phenotype. These M1 macrophages produce inflammatory cytokines that inhibit the ability of adipocytes to respond to insulin. Conversely, weight loss is associated with a reversal of this shift (with M1 macrophages transitioning back to the anti-inflammatory M2 phenotype). The researchers indicate that obesity plays a significant role in insulin resistance due to the number and phenotype of involved macrophages (4). Macrophages also express Dectin-1 at a high level, which increases the production of pro-inflammatory cytokines. Dectin-1 as a receptor of innate immune cells is involved in various cellular responses such as chronic inflammation, autoimmune diseases and diabetes (5). This receptor is highly expressed on monocytes, macrophages, neutrophils and other immune cells. Impairment in the function and expression of Dectin-1 is associated with the development of inflammatory diseases (6). The data of previous studies show that Dectin-1 may be one of the important indicators in the development of insulin resistance and inflammation caused by obesity because Dectin-1 is expressed on macrophages and modulating their function and phenotype in the development of obesity and insulin resistance is involved (7). The role of various immune cells in metabolism has been established. Phenotypic changes in macrophages may help reduce the development of inflammatory diseases, and with the role of exercise on adipose tissue, chronic exercise appears to inhibit macrophage infiltration into adipose tissue by decreasing mRNA expression of F4/80. Furthermore, exercise may increase the expression of M2 markers and decrease the expression of mRNA for TNF- α and TLR4, which activate the inflammatory pathway NF- κ B. Chronic exercise modulates TLR4 signaling and also suppresses the production of IL-12, interferon γ inducer, β 2-adrenergic receptors in monocytes and macrophages (8). Exercise suppresses M1 markers and potentially induces M2 markers in monocytes through PPAR γ -stimulated signaling, which may help improve systemic insulin sensitivity in athletes. There are findings that suggest an alternative mechanism by which exercise may exert its anti-inflammatory effects to prevent insulin resistance and type 2 diabetes. One of the mechanisms by which exercise may be effective is through its anti-inflammatory effect. For example, in response to exercise, IL-6 derived from muscle causes an increase in the levels of anti-inflammatory cytokines such as IL-10 and the IL-1 receptor antagonist (IL-1Ra) (9). Researchers have reported that resistance exercise is associated with reducing the risk of low-grade chronic inflammation and improving metabolic diseases such as cardiovascular disease and type 2 diabetes (10). Although the mechanism of these changes is not clear, it appears that resistance exercise leads to changes in the production of pro-inflammatory and anti-inflammatory cytokines, which improves insulin resistance and is influenced by the intensity of the activity. Physiological stress due to heavy resistance exercise acts as a strong stimulus in muscle hypertrophy and control of inflammatory responses (11). Therefore, finding the appropriate intensity and type of these exercises to improve

inflammation can provide new insights into therapeutic goals for obese individuals. In this study, high-intensity functional exercises, which are a relatively new training method and focus on functional, multi-joint movements, are used. Typically, a cross-fit training regimen is used in high-intensity functional exercises. Functional exercises are usually full-body exercises that affect the entire body, such as deadlifts, snatches, and squats (12). Therefore, this study aims to investigate the effect of a period of high-intensity functional exercise on IL-10, IL-1Ra, and Dectin-1 in pre-diabetic obese women.

Methods

The present study employed a semi-experimental pre-test and post-test design with a control group. Thirty eligible volunteers between the ages of 35 and 40 were selected for the study. Inclusion criteria required participants to be non-addicted to drugs or alcohol, with a BMI above 28, a waist-to-height ratio (WHtR) greater than 0.5, and no physical injuries or conditions that would preclude their participation. After undergoing a physician's examination, eligible participants were enrolled in the study. Before participating, all study procedures and methods were fully explained to participants, and written consent was obtained after they completed a medical questionnaire. The study was conducted by ethical guidelines, as indicated by the IR.IAU.SARI.REC.1401.133 code.

Participants with fasting blood sugar levels ranging from 100-125 mg/dl, 2-hour postprandial blood sugar levels ranging from 140-199 mg/dl (measured after consuming 57 grams of glucose), and hemoglobin A1c (HbA1c) levels ranging from 4.6-7.5 were considered to be in the pre-diabetes stage. Participants were homogeneously divided into two groups: 1) control (15 individuals) and 2) high-intensity functional exercise based on CrossFit (15 individuals). The training protocol was based on the study by Fito et al. and the entire training period lasted for 16 weeks, with each session lasting approximately 60 minutes. The high-intensity functional training sessions were supervised by a resistance training coach and included a range of exercises, such as squats, deadlifts, presses, halteres, dumbbells, medicine ball exercises, fixed weight exercises, kettlebell swings, aerobic exercises (such as running, jumping rope), weight-bearing exercises (such as horizontal stretching, squatting), and weightlifting exercises (such as front squats, kettlebell rotations) based on the "Workout of the Day" (WOD) protocol (9, 13).

Blood samples were taken from participants 48 hours before and after the 16-week training period from the antecubital vein of their right arm in a sitting position, and 5 cc of blood was collected. The samples were transferred to special laboratory tubes for preparing serum and centrifuged at 3000 rpm for 10 minutes. The obtained serum was kept at a temperature of -70 degrees Celsius. It should be noted that all the stages of the test were conducted in the same and standard conditions at 8 to 10 in the morning. Serum levels of Dectin-1, IL-10, and IL-1Ra were measured by ELISA method.

Descriptive statistical methods (mean, standard deviation, and tables) were used to describe the data. The Shapiro-Wilk test was used to examine the normality of the distribution of study variables, and the appropriate statistical test was selected based on the sample size. Analysis of covariance (ANCOVA) was used to compare the data, with an alpha level of 0.05. SPSS 23 was used for data analysis.

Results

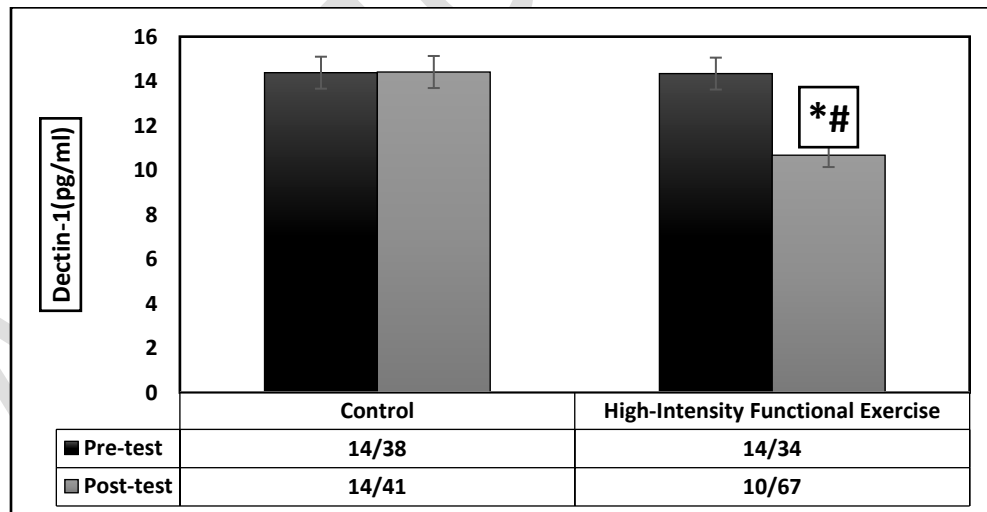
Table 1 presents the mean and standard deviation of the demographic characteristics of the participants. Tables 2 show the mean, standard deviation, percent change, and significance level of the study variables separately for the two groups at different stages (pretest and posttest). The results showed that high-intensity functional exercise based on CrossFit led to a significant increase in the levels of IL-10 ($p < 0.001$) and IL-1R ($p < 0.001$) and a significant decrease in the levels of Dectin-1 ($p = 0.048$) in obese pre-diabetic women compared to the control group (Figures 1-3).

Table 1. Mean and standard deviation related to the individual characteristics of the subjects

Variable group		Control	High-Intensity Functional Exercise
Number		15	15
Age (Years)		37±4	37±3
Weight (kg)	Pre-test	88.11±5.45	87.55±5.69
	Post-test	88.13±5.23	84.65±5.40
BMI (kg/m ²)	Pre-test	30.10±1.01	29.49±1.23
	Post-test	30.14±0.8	27.48±1.05

Table 2. Mean and standard deviation related to the Dectin-1, IL-10 and IL-1Ra levels

Variable	Stage Group	Pre-test (Mean ± SD)	Post-test (Mean ± SD)	Percent Change	Between groups (p-value)
Dectin-1 (pg/ml)	Control	14.38 ± 0/36	14.41 ± 0.73	0.21	P=0/048
	High-Intensity Functional Exercise	14.34 ± 1/24	10.67 ± 0.64	*-25.60	
IL-10 (pg/ml)	Control	3.511 ± 0.12	3.515 ± 0.24	0.11	P<0/0001
	High-Intensity Functional Exercise	3.483 ± 0.15	4.252 ± 0.2	*18.11	
IL-1Ra (pg/ml)	Control	163.93 ± 6.2	164.04 ± 7.23	0.06	P<0/0001
	High-Intensity Functional Exercise	165.95 ± 5.14	194.45 ± 8.26	*14.66	

**Figure 1.** Average Dectin-1 values between two groups *: A significant sign compared to the pre-test stage. #: A significant sign compared to the control group.

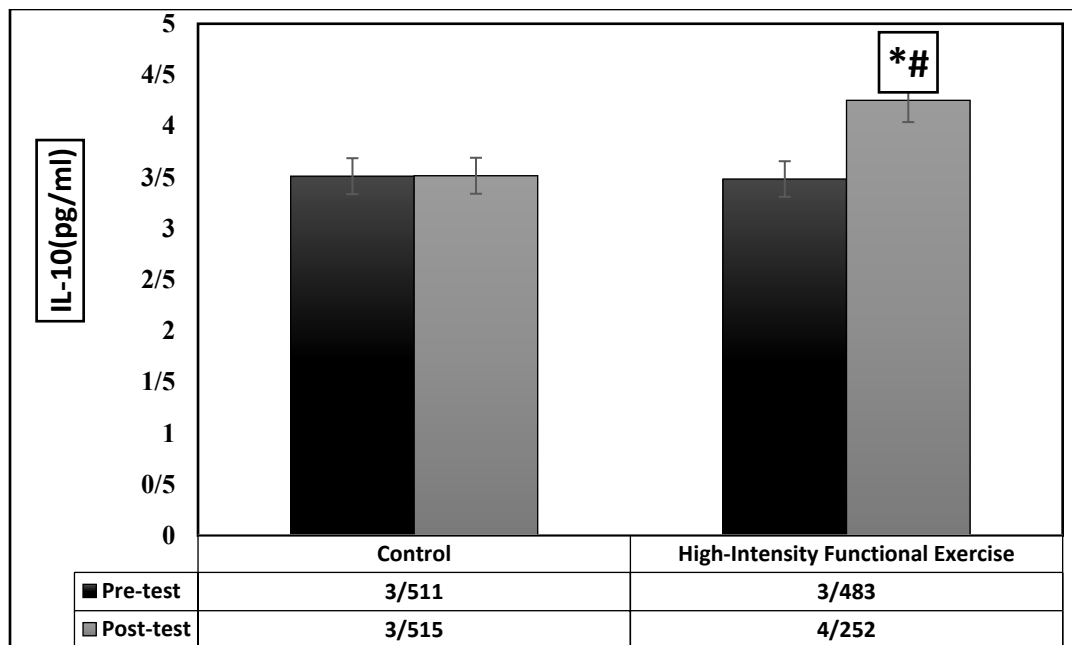


Figure 2. Average IL-10 values between two groups *: A significant sign compared to the pre-test stage. #: A significant sign compared to the control group.

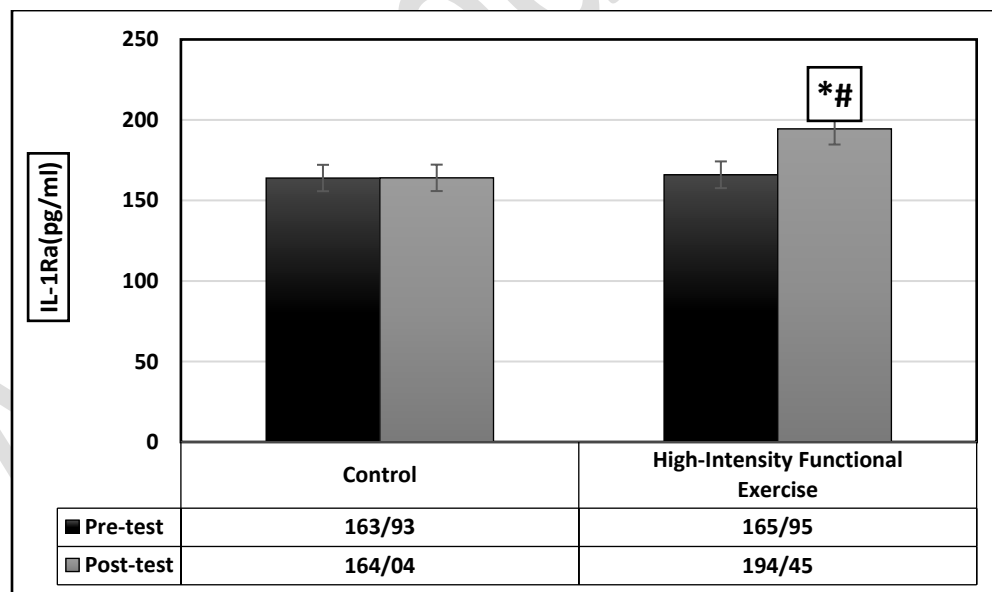


Figure 3. Average IL-1Ra values between two groups *: A significant sign compared to the pre-test stage. #: A significant sign compared to the control group.

Discussion

The results of the present study showed that 16 weeks of high-intensity functional training led to a significant reduction in Dectin-1 and a significant increase in IL-10 and IL-1Ra in pre-diabetic obese women. The increase in interleukin-10 levels in pre-diabetic obese women following high-intensity functional exercises in the present study is consistent with the results of some previous studies (10, 14). Exercise likely directly reduces the production of inflammatory cytokines in adipose tissue, muscle, and mononuclear cells, and indirectly increases insulin sensitivity, endothelial function, and weight loss, ultimately leading to a reduction in pro-inflammatory factors and an increase in anti-inflammatory factors. The anti-inflammatory effects of exercise also depend on the duration and intensity of the exercise. In the present study, it was also found that the increase in IL-10 levels in the high-intensity functional training group was significantly compared to the control group. IL-10 increases in response to increased pro-inflammatory cytokines, to suppress them, and it seems that short-term exercise periods cannot lead to significant changes in the baseline levels of this anti-inflammatory cytokine. One of the reasons for the increase in IL-10 after exercise is the increase in fatty acid oxidation and consequent reduction in adipose tissue, including visceral fat. It has been shown that a decrease in fat mass results in a decrease in macrophage infiltration into adipose tissue and the conversion of M1 macrophages into M2 phenotype monocytes, which leads to an increase in anti-inflammatory cytokines such as IL-10 and a decrease in pro-inflammatory cytokines (15). Another mechanism involved in the increase of IL-10 following exercise is the alteration of interleukin-6 (IL-6) levels during exercise. It has been shown that exercise increases muscle turnover and leads to an increase in IL-6 in muscle and blood. IL-6 itself leads to an increase in IL-10 secretion in macrophages (16). Physical activity can reduce the resting levels of cytokines such as IL-6 and tumor necrosis factor-alpha (TNF- α) and ultimately increase the production of IL-10. Some of these effects may be due to cytokine production from other parts of the body besides adipose tissue, such as skeletal muscles and mononuclear cells. In addition, regular exercise improves endothelial function by maintaining the availability of nitric oxide, reducing the production of atherogenic cytokines (TNF- α and interferon-gamma), and increasing the production of anti-inflammatory cytokines such as IL-10 (17). These multiple effects of exercise convert the balance of resting cytokines to an anti-inflammatory state. Based on molecular mechanisms, exercise negatively regulates the activity of NF- κ B and increases IL-10 secretion through monocytes and T cells via the Th2 pathway (18). However, NF- κ B was not investigated in the present study, which is one of its limitations. The results of some studies are inconsistent with the findings of this study. Rahimian et al. did not observe a significant change in IL-10 levels in obese women after 8 weeks of resistance training at 60 to 85% of one repetition maximum (19). The contradictions reported in the studies can be attributed to factors such as the health status and initial weight of the participants, insufficient duration of the exercise period, and the type of exercise. Another significant finding in the present study was the significant reduction of Dectin-1 after 16 weeks of high-intensity functional training in pre-diabetic obese women. The regulation of the protein Dectin-1 can also be influenced by various cytokines, such as IL-4 and GM-CSF (20). The response of Dectin-1 to exercise and the mechanisms underlying changes in Dectin-1 levels following exercise are not yet well understood. However, it is possible that intense functional training may alter Dectin-1 protein levels through the effects of IL-4 and GM-CSF. Nonetheless, these factors were not examined in the present study, which is one of its limitations. Dectin-1 also requires interferon regulatory factor 5 (IRF5) for immune response, and IRF5 is essential for distinguishing between M1 macrophages and white adipose tissue, which plays a major role in insulin resistance resulting from obesity (21, 22). Additionally, it has been reported that Dectin-1 is activated by vimentin, a cytoskeletal filament expressed in mesenchymal cells (23). Therefore, the effects of exercise on Dectin-1 changes may occur through vimentin. Further studies are needed in this field. The conflicting results reported in studies may be due to different factors, such as diet, exercise program, type of subjects, and exercise duration. Dectin-1 may be a key factor in the development of inflammation and insulin resistance associated with obesity, as it is expressed in macrophages and dendritic cells, and is thought to modulate macrophage function and phenotype, contributing to the development of obesity and insulin resistance (7). In contrast to our findings, Rofino et al. (2016) investigated the effects of an 8-week moderate-intensity exercise program on certain markers in monocytes of sedentary women. Nineteen

sedentary women completed an 8-week moderate-intensity exercise program (45 minutes of walking, three times per week), which significantly increased the expression of Dectin-1 (9). Differences in exercise protocol, measurement site, and duration may lead to different results. However, due to the limited findings in this area, further research is needed. Additionally, the results of the present study showed that a 16-week high-intensity functional training led to a significant increase in IL-1Ra in women with pre-diabetic obesity. Previous studies provide a molecular understanding that neutrophils become transcriptionally activated and respond to a period of severe endurance exercise that includes moderate muscle damage. Potential stimuli for coordinating the expression of performance-related gene groups, including IL-1R and TLR signaling stimuli, and pathways involved in sensing and responding to tissue damage, including muscle-derived components in circulation (e.g., myoglobin), were identified (24). Research indicates an increase in the inflammatory profile of obese samples and a decrease in anti-inflammatory factors such as IL-1Ra, which has been shown to increase with exercise (25). Furthermore, researchers have found that administering IL-1RA alleviates rheumatoid arthritis-related pain. Therefore, it is possible that the downregulation of IL-1R in STZ mice can be attenuated by exercise intervention (26).

Conclusion

According to the findings, it is suggested that 16 weeks of high intensity functional training (HIFT) in order to improve the secretion and function of IL-10 and Dectin-1, IL-1Ra in prediabetic obese women and its benefits in reducing inflammatory complications associated with obesity should be used. One limitation of the study was the lack of measurement of other factors that control lipid metabolism due to high costs in women with pre-diabetic obesity. Measuring other influential variables can provide a better understanding of the effects of exercise. Therefore, it is recommended to pay attention to measuring these indicators in individuals with pre-diabetic obesity in future studies.

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Ethics statement

Before participating, all study procedures and methods were fully explained to participants, and written consent was obtained after they completed a medical questionnaire. The study was conducted by ethical guidelines, as indicated by the IR.IAU.SARI.REC.1401.133 code.

Author contributions

Maryam Enshaei Mojard (First author), principal investigator/protocol implementation (40%), Hajar Abbaszadeh (Second author), methodology author/results interpretation (40%), Parvin Farzanagi (Third author), discussion author (20%).

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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