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# The response of selected adipokines and insulin resistance to interval resistance training with different intensities in men with obesity

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**ABSTRACT**

**Introduction:** This study aimed to evaluate the effect of 12 weeks of interval resistance training with different intensities (low, medium and high) on bone morphogenetic protein 2 (BMP-2), bone morphogenetic protein 4 (BMP-4) and insulin resistance in obese men.

**Materials and Methods:** Forty-four obese not trained men, after determining 1RM and based on anthropometric characteristics were divided into the control, low-intensity interval resistance training, medium-intensity interval resistance training, high-intensity interval resistance training groups (in each group, n=11). The protocol of interval resistance training includes 8 movements which were periodic and in different intensities in the form of 3 Set 10 repetitions with 80% 1 RM, rest between sets active, and with 20% intensity and the number of repetitions 15 in the high-intensity group, in the medium intensity group in the form of 3 sets 13 repetitions with 60% RM, resting active sets with 20% intensity and number 15 repetitions and in the low-intensity group in the form of 3 sets of 20 repetitions with 40% 1 RM, rest between sets was active with 20% intensity and the number of repetitions was 15. The first fasting blood sample was obtained 48 hours before and the second blood sample was collected 48 hours after a twelve-week training period. Then the measurements were performed.

**Results:** The 12 weeks of interval resistance training with different intensities in the training groups led to a significant decrease in BMP-2 and insulin resistance compared to the control group ($P < 0.001$) but for BMP-4 these decreases were not significant ($P = 0.055$).

**Conclusion:** The study showed that different intensities of resistance interval training, especially moderate and high intensity training, can decrease the BMP-2, BMP-4 levels and improve insulin resistance.

**Keywords:** Interval resistance training, Obesity, Adipokine, Insulin resistance

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## Introduction

Obesity is one of the major health problems in the last century and is one of the leading causes of death in developing countries. It accounts for 30% of coronary heart disease and ischemic stroke and approximately 60% of high blood pressure in developed countries is attributed to high BMI resulting in weight gain and obesity (1). When body mass index (BMI) increases, the risk of obesity-related diseases also increases significantly which is associated with higher healthcare costs. In Australia, for example, people with a BMI above 40 pay more than twice as much for health-related expenses as people with a BMI below 25. It should be noted that in addition to the mentioned disorders, the prevalence of obesity is associated with a decrease in quality of life (2). Also, in obese people, with the increase of adipose tissue and obesity, several hormones such as bone morphogenetic proteins (BMPs) are secreted from adipose tissue, which increases diabetes and insulin resistance. Among these BMPs (BMP-2 and BMP-4) are considered new adipokines secreted from adipose tissue. BMPs have received a great deal of attention, and some members of the BMPs family have been shown to induce adipose precursor cells into adipose tissue (3). BMPs are members of the large family TGF-β, which were originally identified as bone-stimulating proteins, but today it has become clear that the activity of BMPs is not limited to bone formation, and various functions have been reported for members of the BMPs family, including, Special attention is paid to the functions of BMP-2 and BMP-4 (4). For example, BMP-4 levels have been reported to increase significantly in obese individuals and patients with metabolic syndrome, and a significant correlation has been observed between most anthropometric and metabolic indices and BMP-4 levels (5). Activation of BMP-4 may be associated with increased adipose tissue in human specimens (6). However, it is not yet known whether BMP-4 acts through endocrine mechanisms or autocrine signaling pathways and whether BMP4 cellular expression reflects circulating BMP4 levels (7), However, serum BMP-4 levels have been reported to be associated with increased human adipose mass, insulin resistance, and metabolic syndrome in non-diabetic patients, and therefore modulation of BMP-4 levels could be a potential therapeutic target for improving obesity-related disorders (4). In addition to BMP-4, increased BMP-2 levels have been shown in overweight and obese individuals, and BMP2 levels may be considered an essential marker for inflammatory conditions (8). Elevated levels of BMP-2 and BMP-4 can also play a role in the invasion and metastasis of cancer cells, and therefore members of the BMP family, especially BMP-2 and BMP-4, are considered sectors for cancer (9). In addition, increased BMP-2 levels in type 2 diabetic patients compared with healthy individuals have been shown to emphasize the role of BMP-2 in the pathogenesis of insulin resistance and increased BMP-2 levels are associated with increased plaque formation and atherosclerosis in diabetic patients (10). One of the ways to control and to some extent treat obesity and related diseases is physical activity. Nowadays, the importance of sports activities in reducing inflammation and inflammatory factors has been increasingly considered (11). Studies have shown that the positive effects of exercise to some extent by regulating the levels of adipokines (reducing the levels of inflammatory adipokines) and increase anti-inflammatory adipokines) (12). Exercise activity increases blood flow, increases capillary density, increases muscle mass, increases glycogen storage capacity due to increased glycogen synthetase enzymes, increases muscle glucose transport protein (GLUT4), improves and accelerates glucose uptake by muscles, improves sensitivity Insulin efficacy, decreased insulin resistance, increased gene expression or activity of

various proteins involved in the insulin signaling cascade, and decreased weight and decreased concentrations of insulin resistance-related adipokines in untrained individuals and those with impaired glucose tolerance and diabetes (13-15). Recently, resistance training or weight training has become a common tool to improve health and increase muscle mass (15). In relate to effect of exercise on the levels of variables studied in the present study, few studies have been done. Researchers have reported for years that regular, aerobic exercise will reduce insulin resistance, obesity and diabetes (16). After conducting several studies, they found that in addition to continuous training, resistance training will also improve insulin resistance and obesity due to increased basal body metabolism as well as muscle metabolism (17). A study reported that combining two types of resistance training and endurance training will have better effects on improving insulin resistance, diabetes and obesity (18). It has also been shown that the effects of high-intensity interval exercise can be very beneficial in improving obesity, diabetes, and related diseases (19). Saeidi et al. (2020) showed that among the three types of resistance training (traditional, circular and interval), interval exercise improved obesity-related adipokines and insulin resistance was observed in obese people with a further decrease in the interval exercise group (20). Therefore, it is very important to pay attention to the effective mechanisms of these exercises so that one of the training intensities of this model of resistance training can be more and better adapted after 12 weeks of training (more impact on adipose tissue, hormones secreted by and insulin resistance on the above indicators. Accordingly, the researcher in the present study for the first time investigated and compared the effect of different intensities of resistance interval on the levels of BMP-4, BMP-2 and insulin resistance in obese men.

## Materials and Methods

Because the subjects of the study were obese men and were examined in a 12-week research project, the present study was a practical and quasi-experimental research. Participants in this study were obese male volunteers who were selected through a call in public and administrative centers. Conditions for entering the research were non-addiction to drugs and alcohol, no history of regular exercise for at least 6 months, no history of kidney, liver, cardiovascular disease, diabetes. The subjects had the BMI = 30, waist-to-height ratio (WHR)> 0.5 and did not have any injuries or physical problems (the subjects examined by a cardiologist). Before participating in the research, all the steps and methods of work were explained to them and after full knowledge and completion of the medical questionnaire a written consent was obtained from all participants. Accordingly, 44 volunteers with an age range of 23-32 years were selected.

In the first session, height and weight were taken from all subjects and all stages of the research as well as how to perform an exercise program with the subjects were shown. In the second session, the subjects were tested for maximum repetition. Then, in another session, the subjects were homogeneously divided into 4 groups based on individual characteristics: 1) control (n=11), 2) low-intensity interval resistance training (n=11), 3) medium-intensity interval resistance training (n=11), 4) high-intensity interval resistance training (n=11).

The one maximum repetition (1RM) of the subjects was calculated using Brzycki equation (22). For the method of determining a maximum repetition, at first, the person warms up with a lightweight and then chooses a weight that can do up to 10 repetitions. If the weight was light and the number of repetitions was more than 10 repetitions, after a little rest more weight would selected so that it can do less than 10

repetitions. The amount of weight and the number of repetitions in each movement were recorded and then placed in the formula.

One maximum repetition = weight (kg) / 1.0278 - (number of repetitions to × 0.0278).

The protocol of interval resistance training included 8 movements of the upper and lower torso (squats, chest presses, knee bends, forearms, leg presses, barbell shoulders, armpits with wire from behind) which were performed periodically and in different intensities.

1. High-Intensity Periodic Resistance Exercise Group: Performing movements (squats, chest presses, knee bends, forearms, leg presses, barbell head, armpit wires from behind) in the form of 3 sets of 10 repetitions with 80% RM, rest between sets Active with an intensity of 20% and several repetitions of 15.
2. Moderate-intensity interval training group: Performing movements (squats, chest presses, knee bends, forearms, leg presses, barbell head, armpit wires from behind) in the form of 3 sets of 13 repetitions with 60% RM, rest between active sets with 20% intensity and 15 repetitions.
3. Low intensity resistance periodic exercise group: Performing movements (squats, chest presses, knee bends, forearms, leg presses, barbell head, armpit wires from behind) in the form of 3 sets of 20 repetitions with 40% RM, active rest sets with 20% intensity and 15 repetitions.

Exercise volume was calculated based on the formula presented by Beechel et al. (1994) (amount of weight × number of repetitions × number of sets = volume of exercise) (35). Rest between sets was considered active for all groups with 20% intensity and 15 repetitions.

The first fasting blood sample was obtained 72 hours before and the second blood sample was collected 72 hours after a twelve-week training period from the subjects' right arm vein. Blood samples were transferred to special plasma test tubes (tubes containing EDETA) and centrifuged at 3000 rpm for 10 minutes. The resulting plasma was stored at -70 ° C. It should be noted that all stages of the test were performed in the same standard conditions from 8 to 10 a.m. The desired indices were measured using the following kits and methods:

HOMA-IR formula (22.5 / fasting plasma insulin * fasting plasma glucose = HOMA-IR) was used to measure insulin resistance (23). BMP-4 using ELISA device and company kit (MyBioSource, USA), catalog number: MBS2514726 and sensitivity Min: 18.75pg / mL; Max: 2000pg / mL was measured. BMP-2 was measured using ELISA and company kit (MyBioSource, USA), catalog number: MBS2506773 and sensitivity 0.47ng/mL.

Finally, descriptive statistics were used to classify and determine the dispersion indices. Kolmogorov-Smirnov test showed that the data have a normal distribution. A correlated t-test was used to compare the number of changes in the pre-test with the post-test in each test group. Repeated two-way analysis of variance and Bonferroni post hoc test was used for comparison between groups. All data were expressed as mean ± standard deviation. All analyzes were performed using statistical software SPSS version 22 and were considered statistically significant ($P < 0.05$).

## Results

Analysis of BMP-4 values of subjects before and after 12 weeks of training using analysis of variance test for repeated measures with intergroup factor showed that the effect of time ($P = 0.002$) is significant and the effect of group-time interaction ($P = 0.055$) is insignificant. Intragroup change of BMP-4 values using a t-dependent test showed that later changes compared to before 12 weeks of training in the control group ($P = 0.82$) and low-intensity training group ($P = 0.30$) were not significant. While these intragroup changes

in the exercise groups with moderate intensity (P = 0.009) and high intensity (P = 0.006) were statistically significant (Figure 1).

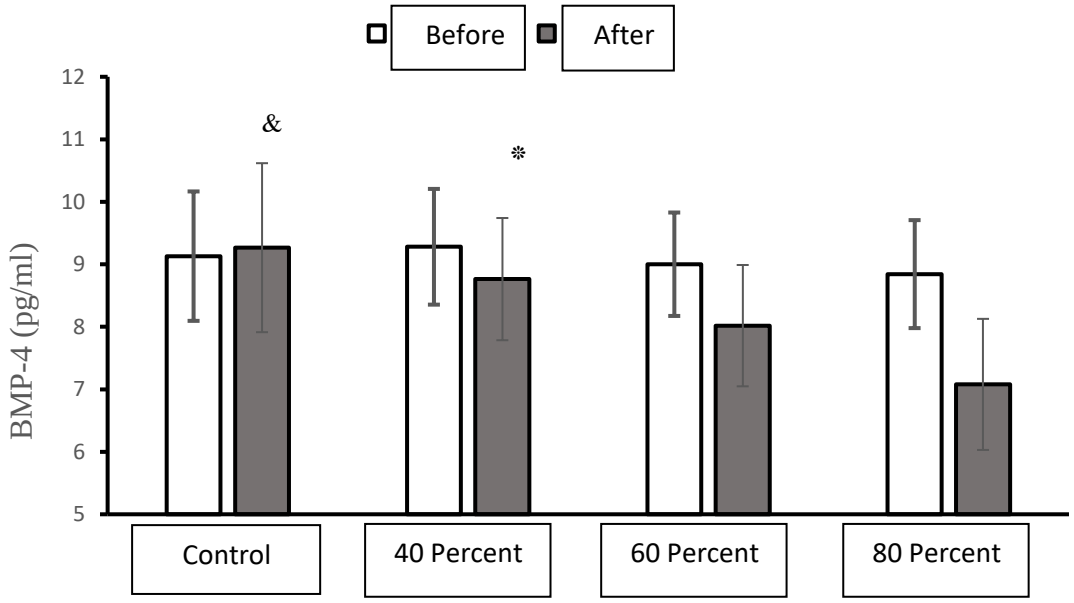


**Figure 1.** Mean ± standard deviation of BMP-4 values of subjects before and after 12 weeks of interval resistance training with different intensities. *Indicates a significant difference between different measurement times, regardless of the intensity of the exercise. &Indicates the differences within the group, in the practice groups with different groups.

Analysis of BMP-2 values of subjects before and after 12 weeks of interval resistance training with different intensities using analysis of variance for repeated measures with intergroup factor showed that the effect of time (P < 0.0001) and time-group interaction (P < 0.0001) are significant. The results of the Bonferroni test showed that between the changes in BMP-2 values of the subjects in the control group with low-intensity training groups (P = 0.002), medium-intensity training (P <0.001) and high-intensity training (P = 0.001) this difference was significant. Intragroup change of BMP-2 values using a t-dependent test showed that later changes were not significant compared to before 12 weeks of training in the control group (P = 0.55) but these changes in low-intensity training groups (P = 0.001), moderate (P < 0.0001) and high (P < 0.0001) were statistically significant (Figure 2). Analysis of insulin resistance values of subjects before and after 12 weeks of training using analysis of variance test for repeated measures with intergroup factor showed that the effect of time (P < 0.0001) And time-group interaction (P < 0.0001) are significant.

The results of the Bonferroni test showed that between the changes in insulin resistance between subjects in the control group with training groups with low intensity (P = 0.013), moderate intensity (P < 0.0001) and high intensity (P < 0.0001) There is a significant difference. Also, the difference between the low-intensity training group and the moderate-intensity training group (P = 0.006) and the high-intensity group (P < 0.0001) was statistically significant, but the difference between the values of insulin resistance in the training group with medium-intensity and high-intensity group were not statistically significant (P = 0.41). Examination of intragroup changes in insulin resistance values using dependent t-test showed that later changes were not significant compared to before 12 weeks of training in the control group (P = 0.27),

while these intragroup changes in training groups with low (P = 0.001), moderate (P < 0.0001) and high intensity (P < 0.0001) were statistically significant (Figure 3).

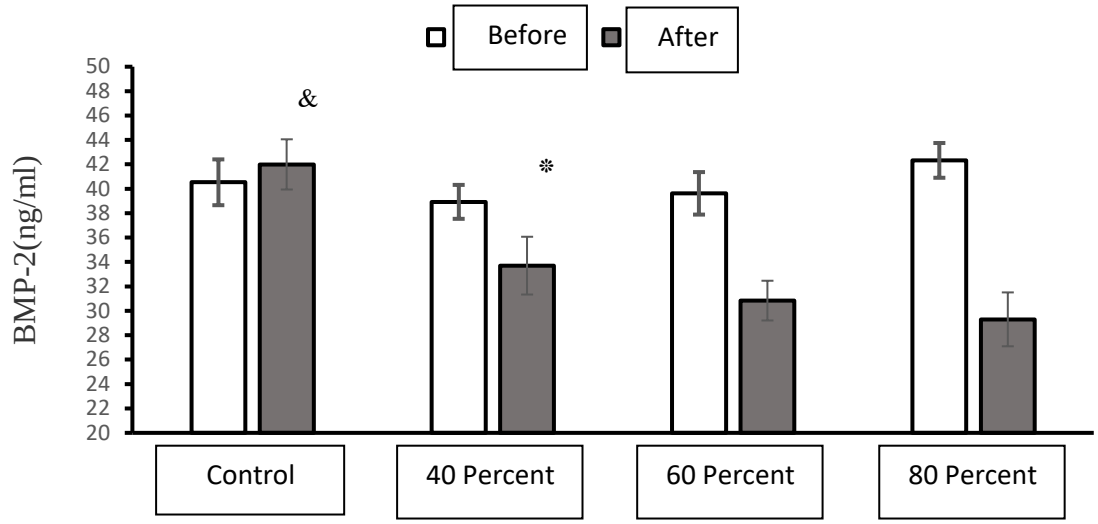


**Figure 2.** Mean ± standard deviation of BMP-2 values of subjects before and after 12 weeks of interval resistance training with different intensities. *Indicates a significant difference between different measurement times, regardless of the intensity of the exercise. &Indicates the differences within the group in different groups.

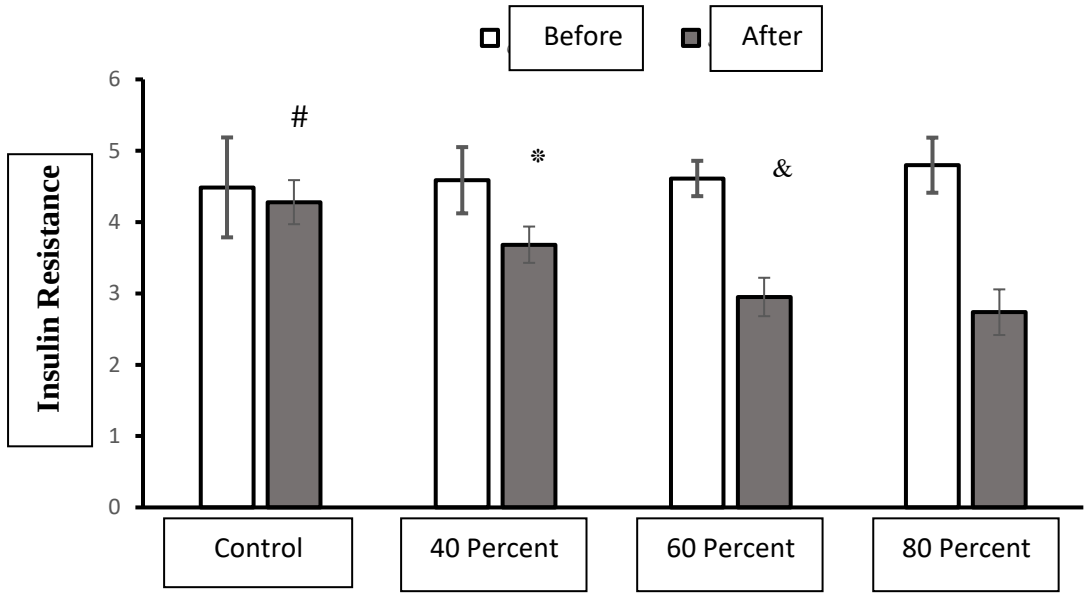


**Figure 3.** Mean ± standard deviation of subjects' insulin resistance values before and after 12 weeks of intermittent resistance training with different intensities. *Indicates a significant difference between different measurement times, regardless of the intensity of the exercise. #Indicates a significant difference between groups. &Indicates intra-group differences in all groups except the control group.

## Discussion

This study aimed to evaluate the effect of 12 weeks of resistance interval training with different intensities on BMP-2, BMP-4 and insulin resistance levels in obese men. The results of the present study showed that the decrease in BMP-2 levels after 12 weeks of resistance interval training with moderate, high and low intensity was significant compared to the control group. In addition, BMP-4 levels in low, medium

and high-intensity groups did not change significantly compared to the control group, but the study of intragroup changes showed a significant decrease in BMP-2 and BMP-4 in resistance training groups with moderate and high intensity.

Obesity is associated with changes in the levels of various circulatory factors, including adipokines (factors secreted by adipose tissue), that BMP-4 can be mentioned as one of these adipokines.

According to studies, BMP-4 is mainly expressed and secreted by adipose tissue and its serum levels increase in obese people. In addition, BMP-4 has been reported to be involved not only in the differentiation of white/beige / brown adipose tissue and thermogenesis, but also in the regulation of systemic glucose homeostasis and insulin sensitivity. Also, decreased BMP-4 function and signaling may play a role in the development of obesity, insulin resistance, and related metabolic disorders (24). Researchers have identified an increase in BMP4 levels as a compensatory mechanism to increase energy consumption (25). These pathological effects of BMP4 are partly due to a decrease in lipolysis as well as a change in gene expression in brown adipose tissue, which may eventually lead to a tendency to change brown adipose tissue to white adipose tissue, which is transmitted through the Smad messenger pathway (25). Some researchers have suggested that BMP4 inhibits beta-cell insulin secretion (26).

Unfortunately, the effect of different types of exercise on BMP4 levels is not known. Majerczak et al. (2020) in a study showed that eight weeks of endurance training in mice with heart failure significantly reduced BMP4 expression in the tibia muscle. However, no significant change in myocardial BMP4 expression was observed (27), indicating a different effect of exercise on BMP-4 expression in different tissues. However, due to the different positions and methods of BMP-4 changes and also the different types of subjects, it is not possible to compare the above findings with the present findings.

Confirming the association between BMP4 and BMP-2 levels with insulin resistance, it has been reported that BMP4 and BMP-2 expression is increased in pancreatic beta cells of diabetic specimens (28). In general, BMP2 / 4 is considered an inflammatory marker in several metabolic tissues (29, 30). Increased BMP4 expression is reflected by increased circulating levels in type 2 diabetic patients (4). Accordingly, systemic inhibition of BMP2 / 4 seems to be a possible strategy to target the low-intensity inflammatory mediators associated with type 2 diabetes, and studies have shown that the induction of anti-BMP4 in animal samples leads to reduce glucose levels (30). The present findings also confirm the negative correlation between BMP4 levels and insulin resistance. Despite the issues raised in the present study as well as the available evidence, the mechanism of action of BMP4 on the pathogenesis of insulin resistance is still largely unclear. Confirming the association between BMP-4 and obesity, it has been reported that BMP-4 levels increase significantly in people with obesity and metabolic syndrome, and its upregulation may play an important role in the pathogenesis of obesity and its metabolic disorders (30). Therefore, modulation of BMP-4 and BMP-2 levels could play an effective role in counteracting the pathological effects of obesity, which should be addressed further in future studies. The present findings showed different intensities of resistance interval training as an effective solution to reduce BMP-4 and BMP-2 levels. However, identifying the mechanism of this impact requires further investigation, which should be considered in future studies.

## Conclusion

The results of the present study showed that interval resistance training with different intensities caused a decrease in insulin resistance, BMP-2 and BMP-4 which this

improvement was greater in the moderate and high intensity groups.

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Study procedures were explained during the first visit, and the Research and Ethics Committee of Tehran University approved all procedures of this study (Ethics code: IR-TU1400-47). The authors thank all the volunteers for their enthusiastic participation in this study.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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