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# The Effect of Eight Weeks Aerobic Training and Omega3 Ingestion on the Levels of CTRP-9 and Adiponectin in Overweight and Obese Women

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**Abstract**

**Background:** Adiponectin and CTRP-9 are adipose tissue secreted adipokines mediating various tissue functions.
**Objectives:** The present study aimed to investigate the effect of eight weeks of aerobic training and omega-3 ingestion on the levels of CTRP-9 and adiponectin in overweight and obese women.
**Methods:** A total of 40 women within the age range of 20-35 years (mean age: 27.29±3.27 years) and mean body mass index of 29.6±1.93 kg.m2 participated voluntarily in the present study. The participants were then randomly assigned into four groups (10 cases per group) of placebo, omega-3, training, and training+omega-3. The aerobic training program lasted eight weeks (three sessions per week); moreover, the omega-3 and training+omega-3 groups consumed 2,000 mg of omega-3 supplements daily. Blood samples were collected pre- and post-intervention (48 h after the last training session or omega-3 consumption). Following that, adiponectin, CTRP-9, and insulin levels were measured by ELISA. Data analysis was performed using the analysis of covariance and Bonferroni post-hoc test.
**Results:** A significant decrease in the CTRP-9 levels and insulin resistance, as well as a significant increase in the adiponectin levels in the training and training+omega-3 groups were observed, compared to the placebo and omega-3 groups ($P<0.05$).
**Conclusion:** Based on our findings, it seems that the positive effects of aerobic training alone or combined with omega-3 supplementation are partially exerted by increased and decreased adiponectin and CTRP-9 levels, respectively. Furthermore, omega-3 supplementation can increase the effectiveness of aerobic training by modulating CTRP-9 and adiponectin levels.

*Keywords:* Adiponectin, Aerobic Training, Obesity, Omega-3

## 1. Background

Obesity is a global health issue that has been remarkably increased in recent decades, and according to the world health organization, obesity and overweight are defined as abnormal or excess body fat accumulation, which negatively affect health (1). Obesity is associated with various pathological effects and increases the risk of different disorders, including cardiovascular and metabolic diseases, and it is suggested that obesity-related metabolic disorders can be attributed to the development of a low-grade systemic inflammatory (2). These findings suggest obesity as a chronic inflammatory condition, and obesity-induced inflammation is due to changes in the expression of cytokines by adipose tissue that has been identified as a major source of secretory proteins that modulate the immune system. These adipose tissue-secreted factors known as adipokines, act as modulators of metabolic and cardiovascular processes (3).

Adiponectin is a well-known anti-inflammatory adipokine, which counteracts the inhibitory effects of cytokines and adipokines on insulin signaling (4). Adiponectin suppresses the secretion of different proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) from adipose tissue and vascular stromal cells, and simultaneously increases the secretion of anti-inflammatory cytokines, including IL-10, and polarizes macrophages toward the M2-type anti-inflammatory phenotype (5). In addition, adiponectin plays an important role in the interaction among obesity, type 2 diabetes, and insulin resistance, and it is reported that both adiponectin and TNF-α inhibit each other's expression and production in adipocytes (6).

Adiponectin belongs to the C1q protein family, which includes more than 30 members, all of which have C1q signature domains (7). Recently, C1q tumor necrosis factor-related proteins (CTRPs) have been discovered as a highly conserved family of adiponectin paralogs, including 15 members from CTRP1 to CTRP15 (8). Some CTRPs play an important role in regulating glucose and fatty acid metabolism *in vitro* and *in vivo*, and among the CTRPs family, CTRP-9 attracted a lot of attention (9). CTRP-9 levels increase in type 2 diabetic patients and have a positive correlation with insulin resistance and body mass index (BMI); moreover, its levels are significantly higher in individuals living with obesity, compared to their non-obese counterparts (10). In contrast to the above-mentioned findings regarding the upregulation of CTRP-9 levels in obesity and type 2 diabetes, some studies have suggested that CTRP-9 could increase lipid metabolism and insulin sensitivity (11), and CTRP-9 can exert protective effects on the cardiovascular system by preventing

cardiomyocyte death during ischemic-reperfusion injury (12).

However, the findings on the effects of CTRP-9 are limited and contradictory. Accordingly, further studies are needed to identify its significant role in chronic conditions, such as obesity.

Exercise affects the circulating adipokines that can decrease inflammatory adipokines (IL-6 and TNF-α) and simultaneously increase the levels of anti-inflammatory adipokines (adiponectin) (13). In addition, the omega-3 supplements can affect the levels of inflammatory mediators (14). Although the effect of omega-3 on CTRP-9 levels is unknown, a significant increase in adiponectin levels in human and animal studies following omega-3 supplementation is observed (15). However, the effect of different types of exercises, especially along with omega-3 supplementation on the levels of CTRP-9 is still unknown. Accordingly, this study aimed to evaluate the effect of eight weeks of aerobic training with or without omega-3 ingestion on the levels of CTRP-9 and adiponectin in overweight and obese women.

## 2. Objectives

The present study aimed to investigate the effect of eight weeks of aerobic training and omega-3 supplementation on the levels of CTRP-9 and adiponectin in overweight and obese women.

## 3. Methods

### *Participants*

A total of 40 overweight and obese women within the age range of 20-35 years were included in this study. The participant's characteristics (age, height, body weight, and BMI) in different groups are represented in Table 1.

**Table1. Participant's characteristics (mean±SD)**

| | P | S | T | TS |
|---|---|---|---|---|
| **Age (years)** | 28.3±3.6 | 26.7±3.1 | 26.2±2.9 | 27.8±3.3 |
| **Height (cm)** | 159.8±4.7 | 158.6±3.3 | 160.4±3.5 | 159.7±3.1 |
| **Weight (kg)** | 74.8±6.1 | 75.1±5.3 | 77.3±4.9 | 74.5±5.8 |
| **BMI (kg.m²)** | 29.2±2.0 | 29.8±1.4 | 30.0±2.1 | 29.2±2.1 |

P: placebo, S: omega-3 supplement, T: training, TS: training+omega-3 supplement

### *Inclusion and Exclusion Criteria*

The inclusion criteria were 1) age range within 20-35 years; 2) no history of cardiovascular diseases, type 2 diabetes, hypertension, cancers, malignancies, and sedentary lifestyle in the last year; 3) no consumption of blood pressure and circulating lipid-lowering medications; and 4) no use of nutritional supplements for at least six months before beginning the present study. On the other hand, the participants who did not take part in blood sampling session (pretest or posttest), those who participated in exercise training or regular physical activity program simultaneous with the present intervention, individuals who had no regular participation in the designed exercise training program, cases who had the physician's advice for interruption or termination of the training program or omega-3 supplementation, those with the incidence of disease during the intervention, and subjects with injuries during the training program were excluded from the study.

### *Study design*

The present study was approved by the Ethics Committee of Science and Research Branch, Islamic Azad University, Tehran, Iran (IR.IAU.SRB.REC.1399.090) and registered in the Iranian registry of clinical trials (IRCT20200810048359N1). All conditions, limitations, disadvantages, benefits, and side effects of the present study interventions, including aerobic training, omega-3 supplementation, or their combination (aerobic training+omega-3 supplement) were explained to the subjects. Ethical principles were considered over eight weeks of the study duration, and subjects could withdraw from the study whenever they wanted. Moreover, the subjects who were still willing to participate in the present research signed the informed consent. Subsequently, the participants were randomly classified into four equal groups (10 cases per group) of placebo (P) (not participating in the aerobic training program, not taking omega-3 supplements), omega-3 supplement (S) (taking omega-3 supplement, not participating in the aerobic training program), aerobic training (T) (participation in the aerobic training program, not taking omega-3 supplements), and aerobic training+omega-3 supplement (TS) (taking omega-3 supplement along with participation in the aerobic training program).

### *Intervention*

The present study interventions consisted of aerobic exercise training, omega-3 supplementation, or both (aerobic training+omega-3 supplementation), in which both of them followed an eight-week protocol.

### *Aerobic training program*

The aerobic training program lasted eight weeks (three sessions per week). Aerobic training intensity was defined as 50%-55%, 55%-60%, 60%-65%, and 65%-70% HRmax in the first two weeks, second two weeks, third two weeks, and last two weeks, respectively (16). Each aerobic training session was about 20 min. Pre- and post-exercise sessions, 10-min warm-up and eight-min cool-down were performed before and after the main exercise. During eight weeks of intervention, the participants in the control group were asked to keep their daily routine life.

### *Omega-3 supplementation*

Omega-3 supplementation (2,000 mg daily) was

considered for S and TS groups, which is an approved dose without any side effects for obese women (17). Omega-3 supplement was consumed as two 1,000 mg capsules in the morning and at night (with or after breakfast and dinner). The P group also consumed 2 g oral paraffin oil daily. Omega-3 supplements were purchased from Karen Company, Iran.

### *Blood sampling and laboratory assessment*

Blood samples were collected at baseline and after completing the eight-week intervention (training, omega-3, training+omega-3). Collected blood samples were poured into a falcon tube and were centrifuged for 15 min at 3000 rpm. Following that, the obtained serum samples were frozen at -80˚C until laboratory assessment. Serum Adiponectin (Biovendor, Catalog Number: RD195023100, Sensitivity: 26 ng/ml), CTRP-9 (Aviscera Bioscience, Catalog Number: SK00081-02, Sensitivity: 1 ng/ml), and insulin (Demeditec Company, Catalog Number: DE2935, Sensitivity: 1.76/IU/ml) levels were measured using ELISA. Glucose levels were also measured by Pars Azmoon diagnostic kit. To measure the body fat percentage, a body composition analyzer (BOCA-X1) was used.

### Statistical analysis

The obtained data were analyzed in SPSS software (version 24). First, the data distribution was determined by the Shapiro-Wilk test, which represented a normal data distribution (P>0.05). Analysis of covariance (ANCOVA) and Bonferroni post-hoc test were utilized to identify between-group differences. Furthermore, within-group differences were determined by paired t-test, and a p-value less than 0.05 was considered statistically significant.

## 4. Results

Between-group analysis indicated a significant difference in terms of BMI and body fat percentage (P<0.001). Moreover, BMI and body fat percentage were significantly different in the T and TS groups, compared to the P and S groups (P<0.001). In addition, the paired t-test revealed a significant decrease in BMI and body fat percentage in the T and TS groups (P<0.001). A significant difference was also noted among the groups regarding homeostasis model assessment-estimated insulin resistance (HOMA-IR) (P<0.001). According to the results of the Bonferroni post-hoc test, a significant difference was noted between T and P (p=0.012), TS and P (P=0.001), and S (P=0.009) groups. In addition, HOMA-IR was significantly decreased in the T and TS groups (P<0.001; Table2).

**Table 2. Variable levels (mean±SD)**

| Variables | Stage | P | S | T | TS | P-value |
|---|---|---|---|---|---|---|
| **BMI (kg.m²)** | Pre-test | 29.2±2.05 | 29.8±1.47 | 30.0±2.11 | 29.2±2.16 | |
| | Post-test | 29.3±2.02 | 29.9±1.49 | 29.5±1.96 | 28.7±2.05 | <0.001 |
| **Paired t-test** | | 0.596 | 0.177 | P<0.001 | P<0.001 | |
| **Body fat percentage** | Pre-test | 91.6±6.85 | 89.7±7.68 | 92.8±6.69 | 92.1±8.08 | |
| | Post-test | 90.8±6.57 | 88.4±5.46 | 90.1±6.04 | 88.9±6.22 | <0.001 |
| **Paired t-test** | | 0.280 | 0.231 | 0.040 | 0.004 | |
| **HOMA-IR** | Pre-test | 1.95±0.35 | 1.87±0.27 | 2.08±0.16 | 1.99±0.27 | |
| | Post-test | 1.90±0.29 | 1.81±0.22 | 1.86±0.22 | 1.76±0.23 | <0.001 |
| **Paired t-test** | | 0.158 | 0.103 | P<0.001 | P<0.001 | |

P: placebo, S: omega-3 supplement, T: training, TS: training+omega-3 supplement

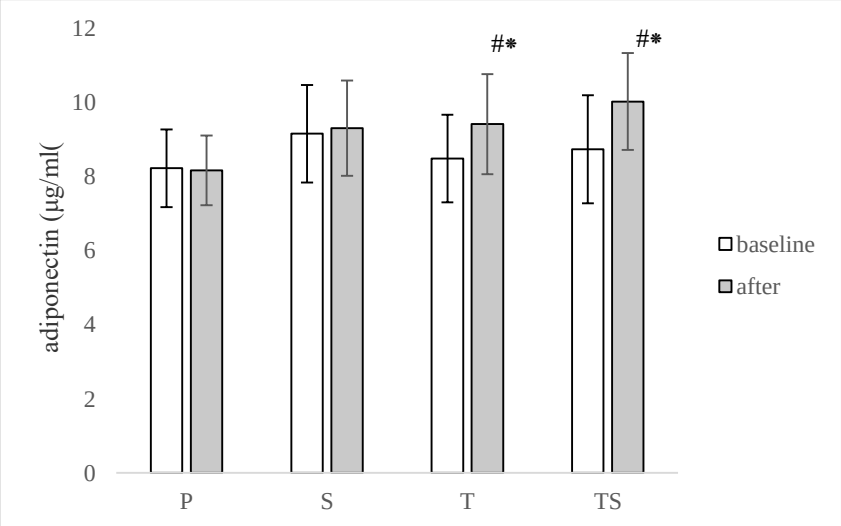


**Figure 1. Adiponectin levels (mean±SD)**
**a significant increase, compared to placebo and omega-3 group**
**# a significant increase, compared to baseline**

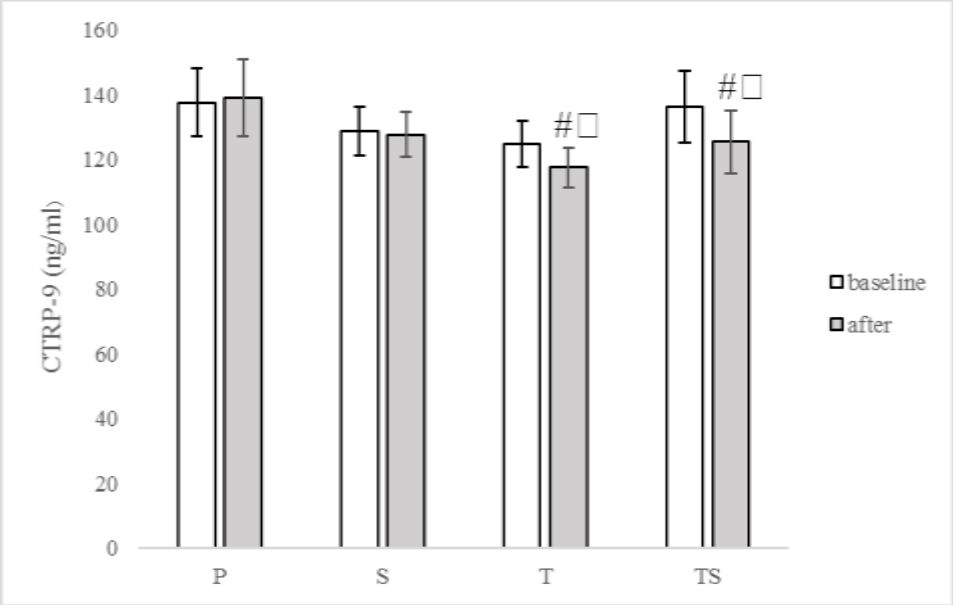


**Figure 2. CTRP-9 levels (mean±SD)**
**∗ a significant decrease, compared to placebo and omega-3 group,**
**# a significant decrease, compared to baseline**

Furthermore, a significant difference was observed between T and P (P<0.001) with S (P=0.008) groups regarding adiponectin levels. This difference was also noted between TS and P with S groups (P<0.001).
Intragroup analysis showed a significant increase of adiponectin in the T (P=0.001) and TS (P<0.001) groups; however, the observed changes in the P (P=0.394) and S (P=0.388) groups were not significant (Figure 1). In addition, analysis of the CTRP-9 levels represented a significant between-group difference (P<0.001), and Bonferroni post-hoc test indicated a significant difference between T and P (P<0.001) with S (P=0.006) groups, as well as TS, P, and S groups (P<0.001). Moreover, a significant decrease of CTRP-9 levels in the T and TS groups (P<0.001) was observed; however, no significant changes of CTRP-9 in the P (P=0.322) and S (P=0.394) groups were noted, compared to baseline (Figure 2).

## 5. Discussion

The present study aimed to investigate the effect of eight weeks of aerobic training and omega-3 supplementation on the serum levels of CTRP-9 and adiponectin in overweight and obese women. The present findings indicated a significant decrease in the CTRP-9 levels and a significant increase in the adiponectin levels in both aerobic training and aerobic training combined with omega-3 supplementation, compared to placebo and omega-3 groups. In addition, eight weeks of aerobic training alone or with omega-3 supplementation was associated with a significant decrease in insulin resistance, compared to placebo and omega-3 groups. It should be noted that observed changes in adiponectin, CTRP-9, and HOMA-IR were higher (non-significant difference) in training+omega-3 groups, compared to the training group.

CTRPs family members play an important role in regulating lipid and glucose metabolism (18). Adiponectin and CTRPs both belong to the larger C1q family and share general structural features, and among the CTRPs family, CTRP-9 represents the highest amino acid sequence identity (approximately 54%) to adiponectin. Some studies suggested that CTRP-9, such as adiponectin, can improve glucose metabolism and increase insulin sensitivity (9, 11). In contrast, it has been reported that CTRP-9 levels increased in obese middle-aged individuals, and a positive correlation of CTRP-9 levels with BMI, insulin resistance, and HbA1c levels have been reported. On the other hand, bariatric surgery and weight loss is associated with a significant decrease in the CTRP-9 levels, and researchers have identified CTRP-9 levels upregulation in obese subjects as a compensatory mechanism, such as increased insulin levels in obesity and type 2 diabetes (10). Given the fact that adipose tissue is a major source for CTRP-9 secretion, increased levels of CTRP-9 in obese cases, compared to individuals with normal weight is not surprising (19). Consistent with the findings of a study conducted by Wolf et al. (10), who reported a significant decrease of CTRP-9 levels in obese subjects after weight loss (10), the present study indicated that weight loss and a decrease in body fat percentage following eight weeks of aerobic training and training+omega-3 supplementation was associated with a significant decrease in serum CTRP-9 levels.

There is limited information about the effect of exercise on CTRP-9 levels. Hasegawa et al. (20)

reported that eight weeks of aerobic training (pedaling) in middle-aged and elderly men and women decreased the CTRP-9 levels non-significantly (20). Probably, the non-significant decrease of CTRP-9 levels in a study by Hasegawa et al. (20) could stem from different subjects' characteristics, compared to the present subjects. Since adipose tissue is the major source for CTRP-9 secretion, fewer changes in CTRP-9 levels among subjects with normal weight seem reasonable. In this regard and contrary to the present findings, in which a decrease in the CTRP-9 levels was associated with a decrease in body fat percentage, in a study by Hasegawa et al. (20), no significant change was observed in body fat percentage. Moreover, the gender differences can also affect the observed changes in the CTRP-9 levels. Moradi et al. (21) reported that CTRP-9 levels were upregulated in type 2 diabetic patients and observed a significantly higher level of CTRP-9 in women, compared to men (21).

Another finding of the present study was a significant increase in adiponectin levels following eight weeks of aerobic training with or without omega-3 supplementation. In fact, a negative correlation was observed between adiponectin and CTRP-9 levels. Consistent with the present findings, it is reported that CTRP-9 levels in individuals with impaired glucose tolerance and newly diagnosed type 2 diabetes were significantly higher, compared to those with normal glucose tolerance in whom increased CTRP-9 levels were associated with a significant decrease in adiponectin levels.

Furthermore, researchers have concluded that CTRP-9 plays an important role in the pathogenesis of type 2 diabetes, obesity, and insulin resistance (22), and the findings of the present study indicated that decreased CTRP-9 levels were associated with decreased insulin resistance. Kim et al. (23) showed that adiponectin levels were significantly lower in obese individuals than non-obese ones; in addition, 12 weeks of exercise training resulted in a significant increase in adiponectin levels, which was associated with a significant decrease in insulin resistance and body fat percentage (23).

In the present study, upregulation of adiponectin levels was associated with a decrease in insulin resistance. The adiponectin effect in increasing insulin sensitivity is exerted through various mechanisms. Some studies suggested that adiponectin indirectly improved insulin sensitivity throughout the body by decreasing adipose tissue inflammation (5). Some researchers also reported that adiponectin exerted its positive effects in the regulation of skeletal muscle energy metabolism through a variety of mechanisms, including increased glucose uptake by increasing GLUT4 translocation or by insulin stimulation. Furthermore, increasing adiponectin-induced lipid and glucose clearance can result in increased insulin sensitivity by decreasing inflammation and reactive oxygen species production and improving mitochondrial function (24). In addition, animal studies have shown that the inhibition of AdipoR2 in mice causes glucose intolerance and hyperinsulinemia, indicating the importance of AdipoR1 and AdipoR2 in regulating normal glucose metabolism and insulin sensitivity (25). Unfortunately, in the present study, changes in the expression, levels, and function of adiponectin receptors are not determined.

However, Nassis et al. (26) indicated that 12 weeks of aerobic training resulted in improved insulin resistance, independent of changes in body weight, body fat percentage, and adiponectin levels (26). No significant changes in adiponectin levels in a study by Nassis et al. (26) can be attributed to the lack of changes in body fat percentage. Supporting this hypothesis, adiponectin as an adipose tissue secretory adipokine has attracted a lot of attention (27). Regarding the relationship between adipose tissue and adiponectin levels, Racil et al. (28) compared the effect of moderate-intensity continuous training with high-intensity interval training (HIIT) in obese young women. They found that despite a significant increase of adiponectin levels in both trained groups, exercise training induced an increase in adiponectin levels that was higher in the HIIT group and was associated with a greater reduction in body fat percentage in this group (28).

These findings emphasize the importance of changes in adipose tissue for subsequent changes in adiponectin levels, especially in obese individuals.

Another finding of the present study was that omega-3 supplementation had no significant effect on the levels of adiponectin and CTRP-9. However, a significant decrease in the CTRP-9 and a significant increase in adiponectin levels were observed in the TS group. The CTRP-9 levels in T and TS groups decreased 19.84% and 23.96%, respectively. In addition, adiponectin increased by 10.95% and 14.76% in the T and TS groups, respectively. These results indicate that observed changes for CTRP-9 and adiponectin in the TS group were greater, compared to that in the T group; moreover, omega-3 supplementation had a synergistic effect on aerobic training.

Although there is no similar study regarding the effect of omega-3 supplementation with or without exercise training on CTRP-9 levels, a significant increase in adiponectin levels after 12 weeks of exercise training (basketball training program) with or without omega-3 supplementation in inactive girls were observed. Consistent with the results of the present study, the increase in the adiponectin levels was further in the TS group, compared to the T group (29).

Regarding the importance of omega-3 supplementation in increasing the effect of exercise training on adiponectin levels, Khedri and Mogharnasi (30) reported that eight weeks of aerobic training alone and in combination with omega-3

supplementation in 50-70-year-old men did not have a significant effect on adiponectin levels; however, adiponectin levels were non-significantly (8.3%) increased in the TS group. Researchers suggested that the intensity and duration of exercise sessions were not appropriate to stimulate further increases in adiponectin levels (30). In addition, differences in the subjects' characteristics, including age and gender, can be considered for contradictions in findings, compared to the present study. Regarding the importance of gender difference in the observed changes for adiponectin levels, previous research indicated that resting levels of adiponectin were significantly higher in women with normal glucose tolerance, compared to those in men; however, a decrease in adiponectin levels was higher among the female diabetic patients, compared to males, which represented differences in adiponectin response to different metabolic states between men and women (31). However, due to the limited evidence, especially regarding the effect of exercise training along with omega-3 supplementation on CTRP-9 and adiponectin levels, training+omega-3 effectiveness mechanisms needed further investigation.

## Study Limitations

The present study limitation was including the little numbers of participants, not having measured the others related adipokines, no fully control of nutritional status, and different motivation and aim of subjects for take oart in this study.

## Strength of the study

Present study findings suggested that omega-3 ingestion can magnify the positive effect of aerobic training in overweight and obese women non-significantly and longer duration of intervention can be associated with further improvement.

## 6. Conclusion

The present findings showed the positive role of aerobic training alone or combined with omega-3 supplementation in improving insulin resistance in obese women. It seems that insulin resistance improvement is partly exerted through upregulation of adiponectin levels and simultaneous downregulation of CTRP-9 levels. In addition, the present findings indicated that omega-3 supplementation can increase the positive effects of aerobic training non-significantly, which can be clinically important.

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## Conflicts of interest

The authors declare no conflict of interest.

## References

1. Ruiz-Ojeda FJ, Olza J, Gil Á, Aguilera CM. Oxidative Stress and Inflammation in Obesity and Metabolic Syndrome. *InObesity*. 2018; (pp. 1-15). Academic Press.
2. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444(7121):860-7. doi: 10.1038/nature05485. [PubMed: 17167474].
3. Gnacińska M, Małgorzewicz S, Stojek M, Łysiak-Szydłowska W, Sworczak K. Role of adipokines in complications related to obesity. A review. *Adv Med Sci*. 2009; 54(2):150-7. doi: 10.2478/v10039-009-0035-2. [PubMed: 19875356].
4. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest*. 2006; 116(7):1784-92. doi: 10.1172/JCI29126. [PubMed: 16823476].
5. Cheng KK, Lam KS, Wang B, Xu A. Signaling mechanisms underlying the insulin-sensitizing effects of adiponectin. *Best Pract Res Clin Endocrinol Metab*. 2014; 28(1):3-13. doi: 10.1016/j.beem.2013.06.006. [PubMed: 24417941].
6. Shimada K, Miyazaki T, Daida H. Adiponectin and atherosclerotic disease. *Clin Chim Acta*. 2004; 344(1-2):1-2. doi: 10.1016/j.cccn.2004.02.020. [PubMed: 15149866].
7. Ghai R, Waters P, Roumenina LT, Gadjeva M, Kojouharova MS, Reid KB, Sim RB, Kishore U. C1q and its growing family. *Immunobiology*. 2007; 212(4-5):253-66. doi: 10.1016/j.imbio.2006.11.001. [PubMed: 17544811].
8. Seldin MM, Tan SY, Wong GW. Metabolic function of the CTRP family of hormones. *Rev Endocr Metab Disord*. 2014; 15(2):111-23. doi: 10.1007/s11154-013-9255-7. [PubMed: 23963681].
9. Peterson JM, Wei Z, Seldin MM, Byerly MS, Aja S, Wong GW. CTRP9 transgenic mice are protected from diet-induced obesity and metabolic dysfunction. *Am J Physiol Regul Integr Comp Physiol*. 2013; 305(5):522-33. doi: 10.1152/ajpregu.00110.2013. [PubMed: 23842676].
10. Wolf RM, Steele KE, Peterson LA, Zeng X, Jaffe AE, Schweitzer MA, et al. C1q/TNF-related protein-9 (CTRP9) levels are associated with obesity and decrease following weight loss surgery. *J Clin Endocrinol Metab*. 2016; 101(5):2211-7. doi: 10.1210/jc.2016-1027. [PubMed: 26982010].
11. Wei Z, Lei X, Petersen PS, Aja S, Wong GW. Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice. *Am J Physiol Endocrinol Metab*. 2014; 306(7):779-90. doi: 10.1152/ajpendo.00593.2013. [PubMed: 24473438].
12. Kambara T, Ohashi K, Shibata R, Ogura Y, Maruyama S, Enomoto T, et al. CTRP9 protein protects against myocardial injury following ischemia-reperfusion through AMP-activated protein kinase (AMPK)-dependent mechanism. *J Biol Chem*. 2012; 287(23):18965-73. doi: 10.1074/jbc.M112.357939. [PubMed: 22514273].
13. You T, Nicklas BJ. Effects of exercise on adipokines and the metabolic syndrome. *J Diabetes Res*. 2008; 8(1):7-11. doi: 10.1155/2014/726861. [PubMed: 24563869].
14. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*. 2004; 6(6):461-7. doi: 10.1007/s11883-004-0087-5. [PubMed: 15485592].
15. Gray B, Steyn F, Davies PS, Vitetta L. Omega-3 fatty acids: a review of the effects on adiponectin and leptin and potential implications for obesity management. *Eur J Clin Nutr*. 2013; 67(12):1234-42. doi: 10.1038/ejcn.2013.197. [PubMed: 24129365].
16. Sheibani S, Hanachi P, Refahiat MA. Effect of aerobic exercise on

serum concentration of apelin, TNFα and insulin in obese women. *Iran J Basic Med Sci*. 2012; 15(6):1196. doi: 10.22038/IJBMS.2012.4940. [PubMed: 23653851].
17. Dadash Nejad F, Gholami M, Soheili S. The effect of eight-week combined exercise training (resistance-endurance) and Omega-3 ingestion on the levels of fetuin-A and metabolic profile in obese elderly women. *Daneshvar Medicine*. 2019; 27(4): 35-44. [Persian].
18. Shanaki M, Shabani P, Goudarzi A, Omidifar A, Bashash D, Emamgholipour S. The C1q/TNF-related proteins (CTRPs) in pathogenesis of obesity-related metabolic disorders: Focus on type 2 diabetes and cardiovascular diseases. *Life Sciences*. 2020: 117913. doi: 10.1016/j.lfs.2020.117913.
19. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Ge G, Spooner E, Hug C, et al. Identification and characterization of CTRP9, a novel secreted glycoprotein, from adipose tissue that reduces serum glucose in mice and forms heterotrimers with adiponectin. *FASEB J*. 2009; 23(1):241-58. doi: 10.1096/fj.08-114991. [PubMed: 18787108].
20. Hasegawa N, Fujie S, Horii N, Uchida M, Kurihara T, Sanada K, et al. Aerobic exercise training-induced changes in serum C1q/TNF-related protein levels are associated with reduced arterial stiffness in middle-aged and older adults. *Am J Physiol Regul Integr Comp Physiol*. 2018; 314(1): 94-101. doi: 10.1152/ajpregu.00212.2017. [PubMed: 29070503].
21. Moradi N, Fadaei R, Emamgholipour S, Kazemian E, Panahi G, Vahedi S, Saed L, Fallah S. Association of circulating CTRP9 with soluble adhesion molecules and inflammatory markers in patients with type 2 diabetes mellitus and coronary artery disease. *PloS one*. 2018; 13(1): 0192159. doi: 10.1371/journal. pone.0192159. [PubMed: 29381773].
22. Jia Y, Luo X, Ji Y, Xie J, Jiang H, Fu M, Li X. Circulating CTRP9 levels are increased in patients with newly diagnosed type 2 diabetes and correlated with insulin resistance. Diabetes research and clinical practice. 2017; 131:116-23. doi: 10.1016/j.diabres.2017.07.003. [PubMed: 28743061].
23. Kim JY, Kim ES, Jeon JY, Jekal Y. Improved insulin resistance, adiponectin and liver enzymes without change in plasma vaspin level after 12 weeks of exercise training among obese male adolescents. *Korean J Obes*. 2011; 20(3):138-46.
24. Liu M, Liu F. Regulation of adiponectin multimerization, signaling and function. *Best Pract Res Clin Endocrinol Metab*. 2014; 28(1):25-31. doi: 10.1016/j.beem.2013.06.003. [PubMed: 24417943].
25. Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T. Adiponectin receptors: a review of their structure, function and how they work. *Best Pract Res Clin Endocrinol Metab*. 2014; 28(1):15-23. doi: 10.1016/j.beem.2013.09.003. [PubMed: 24417942].
26. Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*. 2005; 54(11):1472-9. doi: 10.1016/j.metabol.2005.05.013. [PubMed: 16253636].
27. Bełtowski J. Adiponectin and resistin--new hormones of white adipose tissue. *Med Sci Monit*. 2003; 9(2):55-61. [PubMed: 12601307].
28. Racil G, Ounis OB, Hammouda O, Kallel A, Zouhal H, Chamari K, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. *Eur J Appl Physiol*. 2013; 113(10):2531-40. doi: 10.1007/s00421-013-2689-5. [PubMed: 23824463].
29. Piroozan F, Daryanoosh F, Jafari H, Sherafati Moghadam M. The Effect of 12-Week Exercise with Omega-3 Supplement Consumption on Serum Level Changes of Adiponectin, Leptin, and Insulin in Girls. *Avicenna J Clin Med*. 2015; 22 (2) :129-136. [Persian].
30. Khedri G, Mogharnasi M. Interaction Effect of 8-Week Aerobic Exercise and Omega-3 Fatty Acid Supplementation on Plasma Adiponectin Concentration. *Zahedan J Res Med Sci*. 2013; 15(3): 36-41. [Persian].
31. Saltevo J, Kautiainen H, Vanhala M. Gender differences in adiponectin and low-grade inflammation among individuals with normal glucose tolerance, prediabetes, and type 2 diabetes. *Gender medicine*. 2009; 6(3):463-70. doi.org/10.1016/j.genm.2009.09.006. [PubMed: 19850242].