# Impact of combined exercise training on plasma concentration of Apelin, resistin and insulin resistance in patients with type 2 diabetics' male

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**Original Article**

## Abstract

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**Introduction:** Apelin and resistin as novel adipokines have insulin-sensitizing effects, which may be associated with decreased blood glucose concentration. In this study, we aimed to investigate the impact of combined exercise training on plasma concentrations of apelin, resistin and insulin resistance in patients with type 2 diabetics male (T2D).

**Methods:** In a quasi-experimental study, 24 males with type 2 diabetes were selected from patients of Golestan Hospital Diabetes Clinic in Ahvaz. Subjects were selected using available sampling method. They were randomly divided into two groups: control (mean age, $41.8\pm4.5$ years, mean weight, $82.3\pm8.9$, n=12), and combined exercise training (CT; mean age, $40.8\pm5.4$ years; mean weight, $83.0\pm9.4$ kg, n=12) groups. Combined training was performed 3 times weekly for 8 weeks. Anthropometric, metabolic parameters and plasma apelin, resistin, insulin, glucose levels and resistance insulin were measured at baseline and at the end of study. Within-group data were analyzed with the paired t test, and between-group effects were analyzed with the Repeated Measures ANOVA.

**Results:** After 8 weeks combined training, plasma apelin significantly increased, While plasma resistin, Insulin, glucose and insulin resistance significantly decreased ($P < 0.05$).

**Conclusion:** Our findings suggest that 8-week of combined training significantly influence plasma apelin, resistin, and significantly improved insulin resistance.

**Key words:** Apelin, Resistin, Insulin Resistance, Circuit-Based Exercise, Type 2 Diabetes

## Introduction:

Adipose-tissue derivatives, known as adipokines, have been involved in the inflammatory mediated metabolic and cardiovascular disorders of type 2 diabetes mellitus (T2DM) (1,2). Among novel adipokines, apelin, a 36–amino-acid peptide, has been described as a beneficial adipokine related to cardiovascular risk factors and type 2 diabetes mellitus (3,4). Apelin is the endogenous ligand of the orphan G-protein–coupled receptor APJ (3).

Although synthesized in several tissues, apelin is expressed and secreted by human adipocytes (5-7).

Several molecular forms, e.g. apelin-13, apelin-17, and apelin-36 are cleaved from the 77-amino-acid prepropapelin precursor (8,9).

Resistin is a member of a secretory protein family, known as resistin-like molecules (RELMs) (10). It was originally named for its resistance to insulin (11). Resistin is expressed in white adipose tissue with the highest levels in female gonadal adipose tissue (12), besides adipose tissue, human resistin is also expressed in other varieties of human tissues. Human resistin mRNA has also been detected in the nonfat cells of adipose depots (13). Resistin was identified as a possible link between obesity and insulin resistance (14). Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes, and is also linked to a wide array of other pathophysiologic sequels including hypertension, hyperlipidemia, atherosclerosis and polycystic ovarian disease (15). A specific complication of diabetes, microangiopathy, includes retinopathy, nephropathy, and neuropathy (16). The development or progression of diabetic microangiopathy could be affected by serum resistin (17).

Insulin resistance, defined as a decreased responsiveness to insulin, is a cardinal feature of type 2 diabetes mellitus (T2DM) and metabolic syndrome (1). It has been shown that apelin plasma levels are increased in type-2 diabetic patients (18). Thus, apelin also could represent a promising target in managing insulin resistance (7). Apelin is expressed in pancreatic islet cells (19,20). It has been shown to regulate glucose-stimulated insulin secretion. Many reports show that apelin is involved in glucose homeostasis (21-23).

Apelin injection could improve glucose tolerance and glucose utilization in insulin-resistant mice (7,22). Insulin sensitivity was diminished in apelin-knockout mice, but could be restored by the injection of apelin (21). The action of apelin to improve peripheral glucose uptake has been shown to take place through the activation of the AMP-activated protein kinase (AMPK) pathway (7,22).

These results suggest an important role of apelin in diabetes, not only as a therapeutic target (24) but also in its application as a biomarker.

By now, pharmaceutical agents (e.g. statins, insulin sensitizers) have mostly exerted favorable effects on circulating adipokine levels (25). On the other hand, non-pharmaceutical interventions (e.g. diet, exercise), which are the cornerstone of T2DM treatment, have shown a great variance of effects on adipokine levels (26). Physical exercise has been recommended world-wide as one of the mainstays of treatment of T2DM, along with diet and medications (27,28). Reduced cardiovascular morbidity and mortality have been associated with increased regular physical activity in the diabetic population (29). Limited studies have indicated that physical activity of, even, moderate intensity ameliorates adipokines such as visfatin, apelin and adiponectin in patients with T2DM (2,30). Thus, the aim of this study is to answer the question: Is 8-weeks of combined exercise training effective on circulating levels of novel adipokine (apelin & resistin) and insulin resistance in patient with type 2 diabetics male?.

## Methods:

In this quasi-experimental study, 24 males with type 2 diabetes were selected from patients of Gholestan Hospital Diabetes Clinic in Ahvaz, using available sampling method. They were randomly divided into two groups: combined exercise group (n=12) and control group (n=12). Including criteria were: type 2 diabetic males, 30 to 50 years old, fasting blood sugar (FBS) < 200 mg/dL, no smoking, no insulin injection, no history of cardiovascular or respiratory diseases or muscular and skeletal problems, inactive life style and VO2 max < 40 mL/kg/minute, no regular exercise within six months prior to the study, no hypoglycemia background at rest or exercise. Excluding criteria were: being absent from exercise sessions for more than two successive sessions, no regular participation in an exercise program except for this study exercise sessions for the exercise group and no regular exercise for the control group. The study population consisted of patients admitted to the clinic of the Department of endocrinology and diabetes, Ahvaz Jundi Shapur University of Medical Sciences of Iran. This study was confirmed in 2014 by Shahid Chamran Univesity of Ahwaz, our Institution Ethics Review Board for human studies and participants signed an informed consent. Furthermore, all participants signed an informed consent form. Subjects were excluded if they had a

known history of stroke or transient ischemic attack, uncontrolled hypertension, severe dyslipidemia, acute or chronic inflammatory disease, or any other serious diseases. The subjects became familiar with the purposes of the study and received required instructions about the study. After that, all participants signed the informed consent form. Volunteers were examined by endocrinology and metabolism super specialists. After basic measurement, exercise invention was performed for eight weeks under the researcher's supervision and, the parameters were measured again after the intervention (post-test).

Weight and body mass indexes (BMI) were measured by body composition analyzer machine, Olympic model 3/3, made in Korea. In this respect, the patients, while fasting, referred to physiology laboratory of Shahid Chamran University and stepped on the analyzer machine with bare feet; the analyzer machine gave the researcher a print of their anthropometric information via sensors on the soles and handles, which were in the hands of the patients.

A blood sample after fasting for 12 h was taken between 9-10 in the morning from each patient in clean tubes containing 10 mg of K2EDTA and centrifuged; plasma was separated and stored frozen at 20 C; and plasma apelin, resistin and insulin were estimated using a elisa method. Plasma apelin, resistin and insulin resistance levels were assayed in 2 phases before exercise and 24 hr after the end of the eighth weeks exercise.Plasma apelin and resistin levels were determined by using an enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, China) for apelin and (Boster, USA) for resistin. Plasma glucose was determined using glucose oxidase-peroxidase/4-aminoantipyrine (GOD-PAP) method (Pars Azmoun, Tehran, Iran). Serum insulin concentrations were determined by ELISA kit (Monobind, USA).Homeostasis Model Assessment-Insulin Resistance (HOMA) index for insulin sensitivity was computed using the following equation (31): HOMA-IR=[fasting glucose (mg/dl) $\times$ fasting insulin ($\mu$IU/ml)]/405.

Exercise Training: Exercise training intervention included a combined training program, which was performed by the patients under the supervision of the researcher. The training program for combined exercise was performed during 8 weeks, 3 sessions each week in club of Ahwaz, Iran. The training program for combined exercise was performed during 8 weeks, 3 sessions each week in club of Ahwaz, Iran. The intensity of the aerobic training program proceeded from 50% to 55% (in the first 2 weeks), 55% to 60% (in the second 2 weeks), 60% to 65% (in the third 2 weeks) and 65% to 70% of maximum heart rate (in the last 2 weeks). The duration of training programs without the warm up and cool-down was 15 min. The intensity of training program was controlled and regulated. All subjects performed a warm up (20 min) and a cool-down (15 min) program in every training session. Before the beginning of the research, the subjects became familiar with the training procedure.Work out exercises were performed for different muscle groups (including chest, deltoid, big back, biceps, triceps, thighs, legs and trunk muscles; muscles of the abdomen and back) in three sets; each set included the abovementioned muscles, which was designed according to the recommendations of American Diabetes Association (32). The intensity of exercise was calculated based on the percentage of maximum strength, using Brzycki equation (33); in the first week, patients started exercise with 30-40% of a one-repetition maximum; in the last week, the exercise intensity increased to 60-70% of a one-repetition maximum, given the principle of overload. Each exercise started with 15-20 repetitions in the first week, and the number of repetitions decreased to 8-10 in the last week by gradually increasing the intensity. Duration of the inactive relaxation between the exercises was 40-60 seconds and relaxation between the sets was three to five minutes. Work out was followed by cool down, which included walking quickly for five minutes and stretching exercise (34). The exercise sessions were held in the presence of a nurse. Moreover, the patients were advised to bring sweet snacks to have in case of probable hypoglycemia. Before every session of exercise, the patient's blood sugar and blood pressure were checked using glucometer and digital barometer, respectively.

Statistical Methods: All Statistical analyses were performed with SPSS program (version 19, SPSS, Inc., Chicago, IL). Values were expressed as mean $\pm$ standard deviation (SD). The Kolmogorov-

Smirnov test was used to determine the normality of distribution, and variables were found to be normally distributed. Independent sample t-test was used to evaluate Homogeneous groups at baseline. Repeated Measures ANOVA was used to evaluate differences within groups and between groups. Pvalues less than 0.05 were considered statistically significant.

## Results:

Anthropometric and biochemical characteristics of subjects are shown in Table 1. Results showed that prior to intervention, all variables were homogeneous (Table 1). After 8 weeks combined

training plasam apelin significantly increased, While plasma resistin, Insulin, glucose and insulin resistance significantly decreased (P<0.05). Also, comparing the between groups differences showed that all variables in two groups have significant differences (Table 2).

### Table 1: Anthropometric and Biochemical characteristics of subjects at Baseline

| Group/characteristics | Control | Training | P value |
|---|---|---|---|
| Age (years) | $41.75 \pm 4.5$ | $40.83 \pm 5.4$ | 0.655 |
| Duration of diabetes (years) | $5.04 \pm 1.6$ | $5.29 \pm 1.6$ | 0.716 |
| Weight (kg) | $82.25 \pm 8.9$ | $83.0 \pm 9.3$ | 0.842 |
| Height (cm) | $175.83 \pm 5.6$ | $174.16 \pm 6.1$ | 0.493 |
| BMI (kg.m$^{-2}$) | $26.08 \pm 1.8$ | $26.43 \pm 1.9$ | 0.667 |
| VO$_{2max}$(ml.kg$^{-1}$.min$^{-1}$) | $34.40 \pm 3.14$ | $33.4 \pm 2.5$ | 0.406 |
| Apelin (ng. ml$^{-1}$) | $0.712 \pm 0.1$ | $0.698 \pm 0.1$ | 0.267 |
| Resistin (ng. ml$^{-1}$) | $9.97 \pm 1.4$ | $9.71 \pm 2.0$ | 0.358 |
| Insulin ($\mu$IU. ml$^{-1}$) | $11.16 \pm 3.2$ | $10.54 \pm 6.5$ | 0.581 |
| Glucose (mg. dl$^{-1}$) | $167.41 \pm 17.8$ | $176.71 \pm 40.9$ | 0.670 |
| HOMA-IR | $4.29 \pm 1.2$ | $4.00 \pm 1.3$ | 0.342 |

Data are mean $\pm$ SD. No significant differences were observed between groups (P> 0.05).

### Table 2. Compares difference between and within groups after 8 weeks of training

| Group / Characteristics | Post test | | P-value within groups | | P-value between groups |
|---|---|---|---|---|---|
| | Control | Training | Control | Training | |
| Apelin (pg. ml$^{-1}$) | $0.765 \pm 0.9$ | $0.901 \pm 0.1$ | 0.267 | 0.001† | 0.005* |
| Resistin (ng. ml$^{-1}$) | $10.11 \pm 1.1$ | $8.2 \pm 1.9$ | 0.787 | 0.012† | 0.001* |
| Insulin ($\mu$IU. ml$^{-1}$) | $11.31 \pm 3.1$ | $6.48 \pm 2.2$ | 0.581 | 0.029† | 0.001* |
| Glucose (mg. dl$^{-1}$) | $169.76 \pm 18.1$ | $136.34 \pm 24.4$ | 0.760 | 0.004† | 0.001* |
| HOMA-IR | $3.98 \pm 1.3$ | $2.49 \pm 0.7$ | 0.342 | 0.019† | 0.003* |
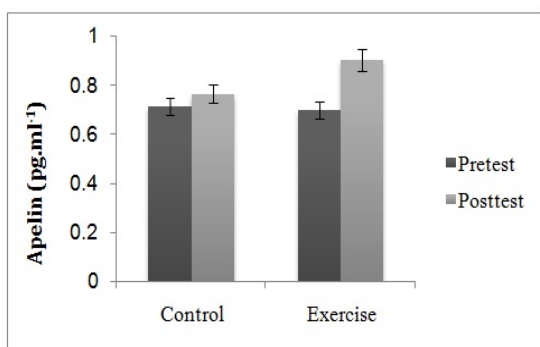
**Figure 1. Plasma consentraion of apelin: mean (±SD) Plasma consentraion of apelin in control and exercise group, pretest and postest**
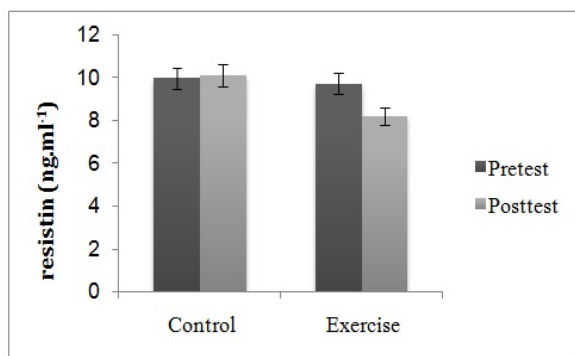


**Figure 2. Plasma consentraion of resistin: mean (±SD) Plasma consentraion of apelin in control and exercise group, pretest and postest**
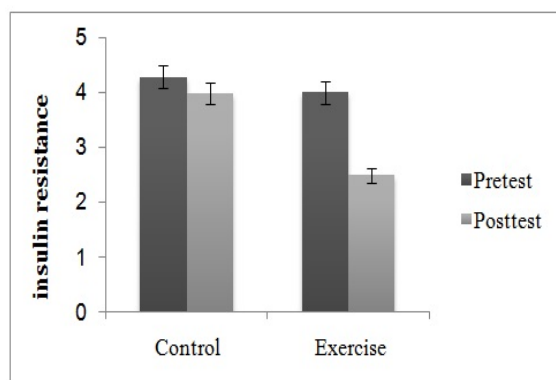


**Figure 3. Insulin resistance: mean (±SD) insulin resistance in control and exercise group, pretest and postest**

## Conclusion:

In this study, after eight weeks of combined training, plasma glucose levels, insulin and insulin resistance in exercise group compared to the control group were significantly reduced. Also, plasma apelin in exercise training group compared to the control group was significantly increased.

Findings of previous studies have shown that exercise training leads to an increase in plasma concentration of apelin in patients with type 2 diabetes (26,30,35,36). Kadoglou et al (2007, 2012) who showed long term regular physical activity increases significantly serum apelin level and reduces insulin resistance in pateints with T2D (2,26). Also, Amini Lari et al. (2014) showed that 12 weeks of resistance training increases significantly plasma concentration of Apelin and reduces insulin resistance in the elderly overweight women with type 2 diabetes (35). In addition, Kazemi et al. (2014) showed that 8 weeks regular aerobic training increases significantly plasma level of apelin and reduces insulin resistance in diabetics mice (36). On the other hand, Nikseresht et al. (2015) documented a considerable increment in apelin concentrations and reduction of insulin resistance after a 12-week interval training in middle-aged obese men (37). This finding is in accordance with the recent study findings (26,30,35,36). Against, Kloting et al. (2008) and Mohebi et al. (2013), who showed that 8 weeks regular exercise training decreases significantly apelin levels in women with T2D (38,39). Also, Krist et al. (2013) that showed 8 week exercise training significantly decreases apelin and insulin resistance in in Human Obesity (30). In addition, Daryanoosh et al. (2014) no significant change in levels of apelin and insulin resistance in obese older women with type 2 diabetes after 12 weeks of resistance training was observed (40). This finding is inconsistent with the recent study findings (30, 38-40). Reason of these contradictions could be due to differences in sex, different physical composition, duration of training and type of exercise protocol.

That increase insulin sensitivity due to exercise training could be a reason for an increase in plasma apelin. Also, plasma apelin levels in diabetic patients exercise group were negatively associated with insulin resistance. So that apelin plasma levels

increased in parallel with insulin resistance. The present findings are consistent with the findings of a previous study (26,30,35,36), that apelin as adipokine plays a role in Pathological insulin resistance, and regular exercise with increment in plasma apelin level can improve metabolic parameters in diabetic patients. The two mechanisms to regulate insulin sensitivity through apelin, suggested as follow: 1- Apelin increases consume glucose directly through the APJ signaling pathway and activation of Gq connection with adenosine mono-phosphate-activated protein kinase (AMPK) and endothelial nitric oxide synthase (eNOS) (7). It has been shown that hemodynamic factors involved in glucose consumption, so that the Decoding vessel increases the sensitivity to insulin and Artery stenosis reduces glucose consumption. Apelin with the release of nitric oxide (NO) causes endothelium-dependent Decoding vessel. However, the lack of effect of apelin in patients and mice lacking eNOS can show interact between hemodynamic and metabolic effects of apelin on consume glucose. The fact that apelin, similare to insulin stimulates the blood flow dependent-NO changes, cannot be ignored. Since eNOS expression in skeletal muscle, NO may act on glucose consuming stimulated by apelin. Taken together, these data suggest that activation of eNOS effect on consume glucose is necessary in order to apply for apelin. On the other hand, AMPK signaling upstream NO is a mediator role in the regulation of glucose metabolism and skeletal muscle fatty acid. In addition, AMPK over Akt is through an independent route of insulin which is necessary for mediating the Apelin function on glucose metabolism. However, apelin stimulated glucose consumption by Insulin-dependent mechanism, so that the apelin is associated with insulin signaling at the level of PI3K / Akt, and through the phosphorylation of Akt, transfer (GLUT4) is mediated by insulin and thus, significantly increases glucose consumption (7,41); 2. Apelin indirectly, by regulating the phosphorylation of hormone-sensitive lipase (HSL) and the reduction of free fatty acids (FFA) circulation, leads to inhibition of lipolysis and reduction of insulin resistance, so that inhibitory of apelin effects on lipolysis via at least two routes Gq and Gi including reduced phosphorylation of

excitatory interdependent HSL (SER -563) mediated by protein kinase (PKA) and increased inhibitory phosphorylation of HSL (SER -565) mediated by AMPK which leads to reduction of the hydrolysis of triglycerides and decreases FFA release into circulation, and thereby controls insulin resistance (22). Of course, hypothesis put forward is that apelin can indirectly influence on skeletal muscle metabolism and activation of receptor gamma co-activator that with the proliferation of peroxisomes an alpha (PGC-1α) has been activated, and consequently improves energy metabolism; and mitochondrial biogenesis involves increasing the close correspondence between fatty acid oxidation and carboxylic acid cycle, improves insulin sensitivity (3). Activation of AMPK increases PES-1α expression in skeletal muscle (42). At the same time, PGC-1α involved in energy homeostasis and metabolic functions of insulin sensitivity, plays a role in regulating the apelin expression and secretion, and causes up-regulation of apelin gene expression in plasma and adipocytes (43). So, overall it is likely that apelin beneficially effect on insulin sensitivity through multiple paths to be created. Although the exact mechanisms of how the relationship between apelin levels of exercise and insulin resistance are unknown, activation of AMPK will be the main interface between mediators of insulin sensitivity with exercise and apelin changes (2). So that the up-regulation of AMPK is a strong mechanism for improving insulin sensitivity from exercise training, and it facilitates the entry of glucose into muscle cells with increased expression in skeletal muscle GLUT4 and transfers it to the plasma membrane (44). On the other hand, apelin, through the AMPK and eNOS, stimulates the insulin pathway components such as akt (23); therefore, the exercise training and apelin have similar mechanism to AMPK stimulus and increase energy metabolism, increase glucose metabolism in type 2 diabetic patients, and play an important role to increased apelin levels linked to exercise. Moreover, exercise training increases mitochondrial biogenesis and glycolytic to oxidative fibers change and adapt to exercise by increasing PGC-1α expression in skeletal muscle (43). However, apelin also stimulates PGC-1α and increases mitochondrial biogenesis (42); so, exercise training and apelin have the same and

common mechanism to activation of PGC-1α and improve energy metabolism and insulin sensitivity. Overall, it seems that exercise training, by increasing the effective regulation of apelin, can be a therapeutic target and also an insulin-sensitive factor to reduce and control insulin resistance in the considered type 2 diabetic patients.

Other findings of the present study show plasma resisting levels after eight weeks of combined training in patients with type 2 diabetes significantly was. Balducci et al. (2010) reported that, 12 months regular physical activity reduces resistin in patients with diabetes and overweight (45). Kadoglou et al. (2007), reduced serum resistance and insulin resistance in people with type 2 diabetes after 16 weeks of aerobic exercise with 50% to 85% of VO2max (without weight loss) were observed (46).

Also, Afshounpour et al (2015) reported significant decrease in resistin and insulin resistance level after 24 weeks resistance training in type 2 diabetes patient (47). The results of these studies which all reported significant reduction of resistin and insulin resistance is consistent with result this present study (45-47). On the other hand, tofighi et al (2013) reported no significant changes in serum resistin levels in postmenopausal women with T2D after 12 weeks of combined training (48). Haghighi et al. (2012) investigated the effect of aerobic training on serum resistin level in obese men. Results showed no significant changes in serum resistin levels (49).

The results of these studies which all reported no significant changes in resistin and insulin resistance are consistent with result of the present study (48,49). The difference in the type of subjects, sex, age of the subjects and the duration and intensity of exercise, could be reasons for the lack of alignment with our finding and other research findings. Presgin et al (2006) and Reshidlirmir et al (2011), also, observed increasing resistin after aerobic exercise and concluded that effect of cytokine inflammatory such as IL-6, IL-1 and TNF-α stimulated resistin gene expression in blood mononuclear cells and increased resistin (50,51). These researchers attributed increased resistin to role of this hormone in defending the body against oxidative after aerobic exercise and mentioned resistin response in response to stimulation an anti-oxidant and secretion from blood

mononuclear in response to inflammation. In fact, increased blood levels of inflamatory markers such as resistin, is a protective response against disease (52).

Some features of anti-inflammatory activity may be associated with the produced adipokines adjustment from adipose tissue. In addition, long-term exercise reduced atherogenic adipokines production, while increases production of anti-atehrogenic adipokines (53). Regular moderate exercise, trough decreasing sympathetic stimulation and increasing anti-inflammatory adipokines, inhibits release of inflammatory mediator from adipose tissue which plays an important role in development of chronic disease. May the issue is confirmed about resistin. In association with the reduction of resistin levels after exercise, some studies suggested that the reason is decreasing the anthropometric indices and pro- inflammatory cytokines such as IL-1, IL6 and TNF-α, since this cytokines stimulated resistin gene expression in blood mononuclear cells (54). On the other hand, resistin, in addition to adipose tissue, is also produced from blood mononuclear cells and leukocytes (55). Therefore, it may exercise decrease in plasma resistin levels by anti-inflammatory properties.

This study also suggested that 8 weeks combined exercise training had a significant impact on insulin resistanec. Due to the possible association of resistin with insulin resistance index in humans, insulin resistance changes in this study may be due to changes in resistin levels. Of course, there are conflicting evidences about existing association between resistin serum concentrations and insulin resistance index. As some studies showed, there are relations between resistin with body fat mass and insulin resistance index, but other studies observed no relations between resistin gene and body weight or insulin sensitivity (56,57). Afshounpour et al. (2015) reported significant decrease in insulin and insulin resistance level after 24 weeks resistance training in type 2 diabetes patient (47). Also Friedenreich et al. (2011) reported reduction insulin resistance in postmenopausal women after 6 and 9 weeks aerobic training (58). Davidson et al. (2009) also observed improvement of insulin resistance in men after 6 months aerobic exercise (59). Bahrami et al. (2012) stated insulin resistance indicators

decreased in aerobic training and calorie restriction after 12 weeks training (60). On the other hand, comparing the relation between resistin and insulin resistance in vivo and vitro studies, previous studies on mice have shown that injection of resistin led to insulin sensitivity disorder (10).

Although this study was to gain control of diet program, but it seems that the diet restrictions, such as lack of control over the whole period, as well as on other non-sports activities, do not exercise absolute control. For a full understanding of the mechanisms involved, the results of this study need to be investigated more accurately in the future. In summary, this study found that 8 weeks of the study and exercise combination in middle-aged men with type 2 diabetes, due to the lack of status, change body composition by increasing levels of plasma apelin, reduce the amount of resistin in insulin resistance and an improve was accompanied.

## Acknowledgment:

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