

Original Article

The interactive effect of aerobic-resistance training and estrogen therapy on metabolic syndrome indices and omentin-1

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Abstract

Introduction: Obesity and visceral fat accumulation after menopause are associated with insulin resistance and cardiovascular diseases. We investigated the interactive effect of aerobic-resistance training and estrogen replacement therapy on visceral fat, omentin-1 and HOMA-IR in ovariectomized rats.

Materials and Methods: Fifty female Wistar rats were ovariectomized (OVX) and divided into 5 groups (n=10 rats per group): Ovx+sedentary (Sedentary), aerobic-resistance training (Ovx+Exe), aerobic-resistance training+estrogen replacement therapy (Ovx+Exe+Est), estrogen replacement therapy (Ovx+Est) and sesame oil (Ovx+Oil). The exercise consisted of 8-week aerobic-resistance training (20 m/min, 3 days/week, 60 min/day, 10% slope, Load; 3% body weight). 17 β -estradiol valerate (30 μ g/kg bw; in 0.2 ml sesame oil) were injected subcutaneously, three days a week during 8 weeks; and the Ovx+Est+Est received both exercise protocol and estradiol as previous groups. Obtained data were analyzed by ANOVA and post hoc Tukey test.

Results: Omentin-1 showed significant increase in Ovx+Exe compared to Ovx+Exe+Est and Ovx+Est (P<0.05). HOMA-IR and visceral fat was decreased in Ovx+Exe, Ovx+Exe+Est compared to Sedentary (P<0.05).

Conclusion: Eight-week aerobic-resistance training, 17-b estradiol replacement and co-treatment of exercise+estrogen successfully decreased visceral fat and insulin resistance probably via elevation in omentin-1 in ovariectomized rats. Regarding the risk of hormone replacement therapy this study suggests that 2- month aerobic-resistance training is more effective in treating metabolic syndrome, rather than estrogen replacement therapy.

Keywords:

Combined Exercise;
Hormone Therapy;
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Introduction

Different therapeutic method exist such as exercise, diet

and hormone replacement therapy in order to prevent obesity-related consequences in postmenopausal women (Christiansen et al., 2009). Hormone replacement therapy (HRT) in postmenopausal women

reduced abdominal fat (Kanaley et al., 2001) and insulin resistance (Kanaley et al., 2001, Saengsirisuwan et al., 2009). However, there are inconsistencies on THE EFFECT of estrogen therapy; And Speculations are abounding as to whether it actually increases insulin resistance or has no effect at all.

Moreover, hormone replacement therapy carries the risk of endometrial and breast cancer (Zoth et al., 2012, Zoth et al., 2010). Therefore, discovering new alternatives to combat accumulation of visceral fat always have had great importance in health/medicine. Studies have shown that endurance exercise training reduces visceral fat and improves insulin sensitivity (Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010). There are only a few studies on Utilizing both HRT and exercise in metabolic syndrome with controversial results. For example Evanz et al., 2001 and Zoth et al., 2012 have reported that exercise training and HRT had independent and additive effects on the reduction of total fat mass, while, Saengsirisuwan et al. (2009) and Green et al. (2004) indicated no apparent beneficial interactive effects of exercise and estrogen on metabolic defects.

Studies revealed that adipokines, have been involved in the initiating of hypercholesterolemia, coronary heart disease, risk of developing type 2 diabetes mellitus and metabolic syndrome (Cai et al., 2009, Gousoy et al., 2010, Jialal et al., 2013). Omentin is one of the newest adipokines preferentially produced by visceral adipose tissue and it is presumed to increase insulin sensitivity in muscle, liver, and adipose tissue (Yang et al., 2006). Previous studies reported that obesity (Yang et al., 2006, Batista et al., 2007), PCOS (polycystic ovary syndrome) (Tan et al., 2008), type 1 and type 2 diabetes (Tan et al., 2010) are associated with decreased omentin level, however, weight loss (Batista et al., 2007), aerobic training (Saremi et al., 2012) and treatment with metformin (Tan et al., 2010) lead to elevation in circulating omentin-1 concentration/levels. On the other hand, higher omentin-1 level was detected in women compared with men (Batista et al., 2007, Slentz et al., 2011). This suggests that estrogen might have a stimulatory effect on the production of omentin (Yang et al., 2006) and its reduction may contribute in the progression of metabolic syndrome. A few studies

considered the effect of exercise on omentin level and reported contradictory results. Saremi et al. (2010) showed that 12 weeks of aerobic training in overweight men resulted in an increase (Saremi et al., 2010); whereas Urbanova et al. (2014) showed no significant effect on serum omentin levels (Urbanova et al., 2014). In rodents, ovariectomy, which results in a dramatic reductions in circulating estrogen levels, is similar to naturally occurring menopause and provides an appropriate research model to mimic the postmenopausal hormonal states in human to study abdominal obesity, lipid metabolism and insulin resistance (Babaei et al., 2010, Damirchi et al., 2010, Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010). To our knowledge, the effects of exercise on visceral fat and omentin-1 level in the absence of estrogen has not been understood yet. Therefore, present study was designed to investigate whether combinations of aerobic-resistance exercise and estrogen replacement therapy would have a preferential effect on improvement of metabolic syndrome and if omentin-1 plays a role.

Materials and methods

Surgery and Experimental protocols

The experiments were conducted according to the policy of Ethics Committee of Guilan University of Medical Sciences. Fifty female Wistar rats were ovariectomized under general anesthesia with an intraperitoneal injection of ketamine (50 mg/ml; RotexMedica, Germany) and xylazine (20 mg/ml; Alfasan, the Netherlands) in a ratio of 4:1, according to the technique described in our previous study (Babaei et al., 2010). Rats were divided into the five following groups (n=10 rats per group): OVX+sedentary (Sedentary); OVX+exercise (Ovx+Exe); OVX+exercise+estrogen (Ovx+Exe+Est); OVX+estrogen (Ovx+Est) and Sesame Oil (Ovx+Oil). So, the study design is experimental.

Body weight, food intake and visceral fat were measured using the accurate to 0.1 g scale (Sartorius, Germany). All rats were weighed twice a week, between 09:00 and 11:00. A Weight average was obtained for each animal. Weekly weight for each animal. To measure the food intake, an equal amount

of food (20 g/day/rat) was given to all rats and their consumption was measured the following day by subtracting the remaining uneaten food from the total food given.

Exercise consisted of running on the rodent treadmill for 3 days/week for 8 weeks. During the first four-week of training, rats progressively ran from 15min/day at 15m/min, 0% slope, 0% load up to 45 min/day at 20m/min, 7% slope, with an extra load (3% body weight) fastened to their tails. Then, rats ran 60 min/day at 20 m/min, 10% slope for the last 4 weeks (Aguiar, et al., 2010). 17 β -estradiol valerate (30 μ g/kg body weight; Sigma-Aldrich, U.S.A.) was dissolved in 0.2 ml sesame oil (Aburaihan Co., Tehran, Iran), and was injected subcutaneously three days a week, for eight weeks. Rats in Ovx+Oil group received the same volume of sesame oil. Rats in Ovx+Exe+Est accomplished/performed both exercise and estradiol protocols for the same time period.

Analytical procedure

After complete anesthesia, blood samples were drawn from the inferior vena cava and serum was separated by centrifugation (3000 rpm for 15 min) and stored at -80° C for later biochemical and hormonal assays.

Estimations

Rat omentin ELISA kit (Shanghai Crystal Day Biotech Co., China, Intra-Assay: CV<10%, Inter-Assay: CV<12%) was used for measuring serum omentin concentration. Serum insulin levels were measured by rat insulin ELISA kit (BioVendor GmbH, European Union, Intra-Assay: CV<5%, Inter-Assay: CV<5%). HOMA-IR, serum glucose, cholesterol, triglyceride, HDL-C and LDL-C were determined like our previous works (Babaei et al., 2010, Damirchi et al., 2010).

After collecting the blood samples, all intra-abdominal fat depots including mesenteric, urogenital and retroperitoneal were dissected out by one experimenter and weighed immediately after dissection to avoid evaporative weight loss. Mesenteric fat pad consisted of adipose tissue surrounding the gastrointestinal tract from the gastroesophageal sphincter to the end of the rectum with special care taken in distinguishing and removing pancreatic cells. Urogenital fat pad included

adipose tissue surrounding the kidneys, ureters, and bladder as well as ovaries, oviducts and uterus. Retroperitoneal fat pad was taken as that distinct deposit behind each kidney along the lumbar muscles.

Statistical analysis

All data are presented as mean \pm standard error. Before statistical analysis, the normal distribution and homogeneity of the variances were tested. Statistical comparisons between groups were performed by one-way analysis of variance test and Tukey's post-hoc test using SPSS 22. Statistical significance was set at $p < 0.05$.

Results

Forty-nine animals completed the intervention protocols. There was no significant difference between groups in body weight, height, BMI and food intake at the beginning of the study (Table 1).

Table 2 shows the metabolic, hormonal and morphometric variables measured after experimental period in different groups.

At the end of the experiment, body weight didn't show significant changes in Ovx+Exe, Ovx+Estand Ovx+Exe+Est groups. Height significantly increased by 4.01 % in Ovx+Exe and Ovx+Exe+Est groups compared to Sedentary rats ($P < 0.05$). BMI was significantly decreased by 9.8 % in Ovx+Exe and Ovx+Exe+Est groups compared to Sedentary rats and 13.73 % in Ovx+Est group compared to vehicle ($P < 0.05$) (Table 2). Visceral fat was significantly reduced by 21.41% in Ovx+Exe and 24/83% in Ovx+Exe+Est groups compared to Sedentary ($P < 0.05$). Although 17 β -estradiol replacement reduced visceral fat by 12.84 % in Ovx+Est group compared to vehicle, it wasn't significant. There was no difference between Ovx+Exe, Ovx+Exe+Est and Ovx+Est groups in body weight, height, BMI and visceral fat changes. Serum omentin level was significantly increased (56.34%) in Ovx+Exe, (35.11%) in Ovx+Exe+Est, (41%) in Ovx+Est and 52.18% in Ovx+Exe+Est compared to respected controls ($P < 0.05$). Generally serum omentin-1 level was higher in Ovx+Exe compared to Ovx+Exe+Est and Ovx+Est ($P < 0.05$) (Figure 1).

Food intake was significantly increased by 26.37 % in

Table1: The morphometric variables at the beginning of study

Variables	Ovx+Exe	Ovx+Exe+Est	Ovx+Est	Ovx+Oil	Sedentary	F	P
N	10	10	10	10	10	-	-
Body Weight (g)	182±2.94	186.7±4.11	181.8 ±6.66	186.9±7.26	186.2±6.18	2/081	0/099
Height (cm)	20	20	20	20	20	-	-
Body mass index (g/cm2)	0.46±0.01	0.45±0.01	0.46±0.02	0.47±0.02	0.47±0.02	2/172	0/104
Food intake (g/Rat/day)	5.7±0.11	5.6±0.42	6.5±0.11	6.4±0.42	6.4±0.84	3/150	0/068

Ovx+Exe, ovariectomized-exercise group; Ovx+Exe+Est, ovariectomized-exercise with 17b-estradiol replacement group; Ovx+Est, ovariectomized with 17b-estradiol replacement.

Table2: The metabolic, hormonal and morphometric variables after eight-week experimental period.

Variables	Ovx+Exe	Ovx+Exe+Est	Ovx+Est	Ovx+Oil	Sedentary	F	P
N	10	10	9	10	10	-	-
Body weight (g)	231.2±21.1	230.8±7.16	215.22±9.47	233.60±13.12	233.67±15.40	2/736	0/041
Height (cm)	22.3±0.67a	22.3±0.67a	22.11±0.33	21.7±0.48	21.44±0.51	4/463	0/004
Body mass index (g/cm2)	0.46±0.03a	0.46±0.02a	0.44±0.02 b	0.50±0.04	0.51±0.02	8/760	0/000
Food intake (g/Rat/day)	8.89±0.42a	7.9±1.7	8.05±0.48	7.77±1.26	6.37±0.35	4/974	0/002
Visceral Fat (g)	6.9±1.29a	6.6±0.97 a	6.78±1.05	7.9±1.73	8.78±0.97	5/529	0/001
Glucose (mmol/l)	162.4±12.58a	160.24±18.11ab	164.04±17 b	335.89±19.33	435.4±7.44	622/174	0/000
Insulin (µU/ml)	1.7±0.42a	1.53±0.33 ab	1.97±0.61 b	2.6±0.32	2.49±0.27	13/413	0/000
Cholesterol (mg/dl)	147.42±5.83	149.9±10.38	154.51±12.86	158.68±6.29	158.31±7.9	3/063	0/189
Triglyceride (mg/dl)	89.18±20.35	95.74±5.64	97.97±4.58	105.37±28.75	102.57±15.37	1/241	0/308
HDL-C (mg/dl)	72.85±2.3	72.66±2.97	72.10±3.02	71.19±5.22	70.94±2.29	0/625	0/648
LDL-C (mg/dl)	67.85±2.3	69.22±13.86	73.89±2.63	80.62±19.94	77.99±6.06	2/238	0/081

Ovx+Exe, ovariectomized-exercise group; Ovx+Exe+Est, ovariectomized-exercise with 17b-estradiol replacement group; Ovx+Est, ovariectomized with 17b-estradiol replacement; ^a p<0.05 vs. Sedentary group; ^b p<0.05 vs. Ovx+Oil group.

Ovx+Exe compared to Sedentary group (P<0.05; Table2). Glucose was significantly increased in Ovx+Exe and Ovx+Exe+Est by 63% and compared to Sedentary, and by 52 % in Ovx+Est and Ovx+Exe+Est compared to Ovx+Oil (P<0.05; Table2). Insulin was significantly increased in Ovx+Exe (39/22%), Ovx+Exe+Est (38.55 %), Ovx+Est (24.23%) and Ovx+Exe+Est (41.15%) compared to related controls

(P<0.05; Table2). HOMA-IR was significantly increased in Ovx+Exe (74.73%) Ovx+Exe+Est (77.46%), Ovx+Est (62.51%) and Ovx+Exe+Est (72.12%) (P<0.05; figure2). There was no significant difference in serum glucose, insulin concentrations and HOMA-IR between Ovx+Exe, Ovx+Exe+Est and Ovx+Est groups (Figure2). Finally, slight, insignificant changes were observed in lipid profiles after exercise and estrogen

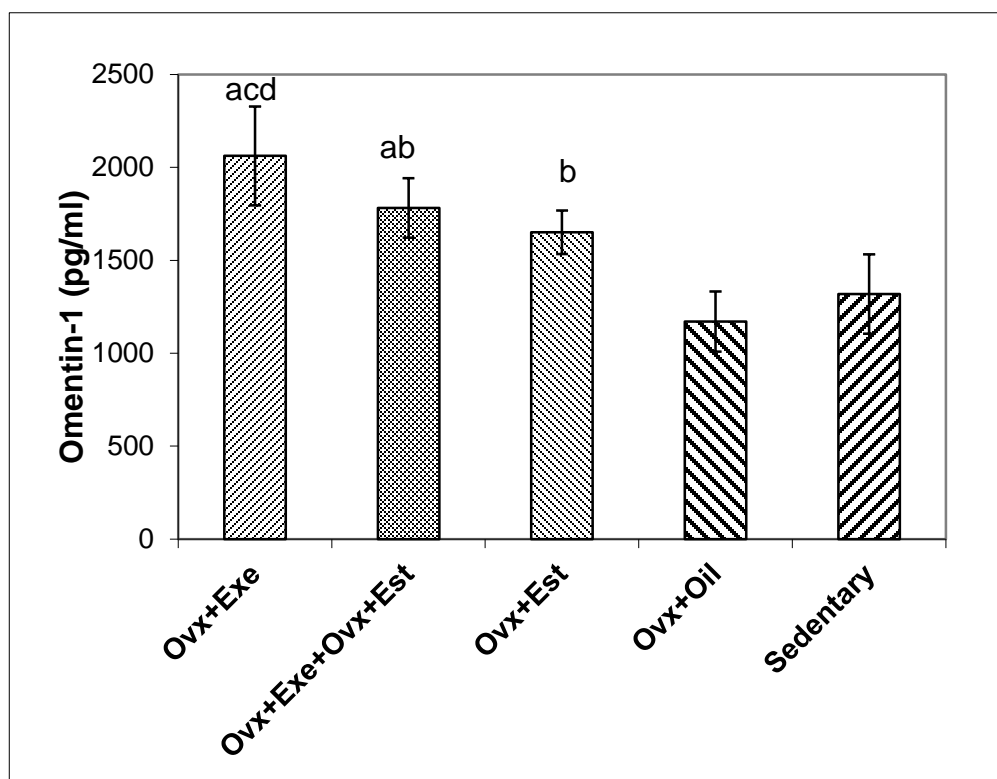


Fig.1. Omentin-1 level after 8 weeks in different groups

OvX+Exe, ovariectomized-exercise group; OvX+Exe+Est, ovariectomized-exercise with 17 β -estradiol replacement group; OvX+Est, ovariectomized with 17 β -estradiol replacement

^a $p < 0.05$ vs. Sedentary group; ^b $p < 0.05$ vs. OvX+Oil group, ^c $p < 0.05$ vs. OvX+Exe+Est group; ^d $p < 0.05$ vs. OvX+Est group.

supplementation (Table2).

Discussion

Our results showed that 8 weeks of aerobic-resistance exercise, exercise-estrogen and estrogen therapy successfully decreased intra-abdominal fat, increased serum omentin-1 level and improved insulin resistance. Surprisingly, exercise per se caused more increases in omentin-1 level compared to co-treatment with estrogen. Elevation in omentin-1 after exercise is in agreement with Saremi and colleagues (2010) STUDIES /Results in overweight men after 12 weeks of progressive aerobic training (Saremi et al., 2010), but Not in agreement with Urbanova and colleagues (2014) in women after 3-month physical activity (Urbanova et al., 2014) . This discrepancy may be, due to difference in subjects (human Vs. animal) and exercise protocol. The finding of increase in omentin-1 after hormone replacement therapy in OvX+Est group is inconsistent with Tan and his colleagues (2008) reporting a negative correlation between omentin-1 level and

circulating 17 β -estradiol (Tan et al., 2008). It is well documented that ovariectomy results in a significant reduction in circulating 17 β -estradiol level and consequently leads to weight gain and an increase in adipose tissue (Babaei et al., 2010, Damirchi et al., 2010, Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010). Probably, the increased omentin-1 in exercise group compared to sedentary might reflect a negative correlation between omentin-1 level and circulating 17 β -estradiol.

Moreover lower serum glucose and HOMA-IR in Exe, Est and Exe+Est groups compared to Sedentary and OvX+Oil are in agreement with other previous studies (Zoth et al., 2012, Zoth et al., 2010). It has been known that fasting and post- prandial glucose, HOMA-IR and fasting insulin levels are negatively correlated with omentin-1 level (Batista et al., 2007, Moreno-Navarrete et al., 2010, Pan et al., 2010). Omentin-1 increases Akt/protein kinase B and enhance insulin-stimulated glucose transport in myocytes and adipocytes (Yu and Gong, 2011) which is an important way to maintain glucose homeostasis (Cai et al., 2009). Therefore

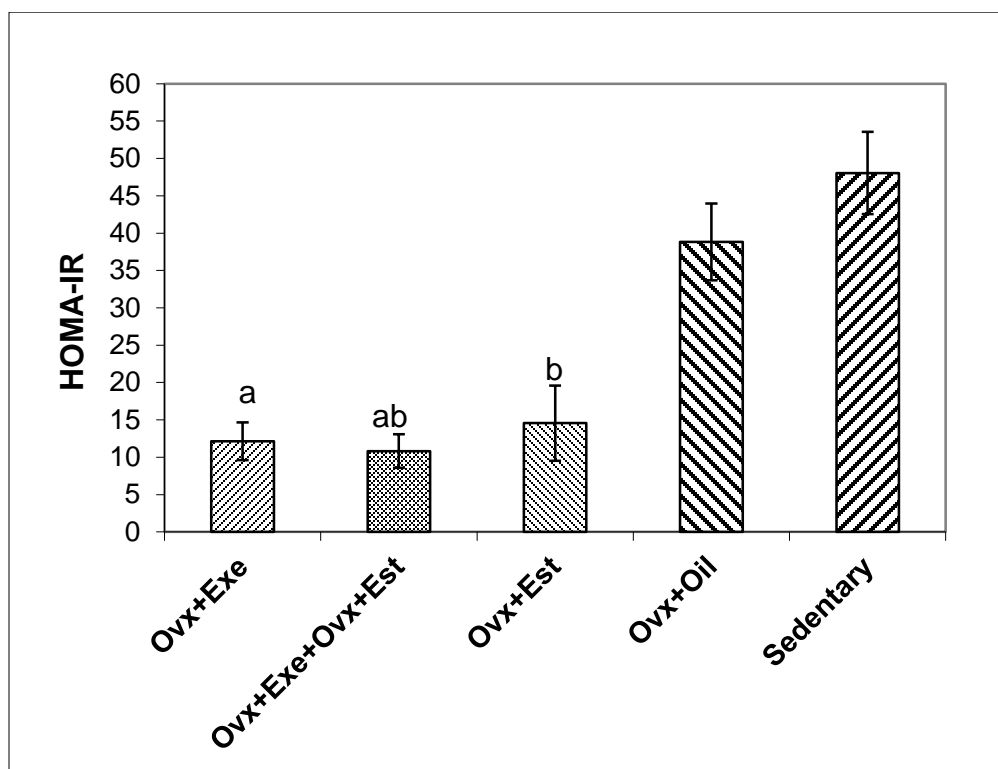


Fig.2. HOMA-IR after 8 weeks in different groups

Ovx+Exe, ovariectomized-exercise group; OvX+Exe+Est, ovariectomized-exercise with 17 β -estradiol replacement group; OvX+Est, ovariectomized with 17 β -estradiol replacement

^a $p < 0.05$ vs. Sedentary group; ^b $p < 0.05$ vs. OvX+Oil group.

reduction in HOMA-IR after 8-week aerobic-resistance training, exercise+estrogen and estrogen replacement therapy in our study may be mediated by omentin-1.

Up regulation of GLUT4 in postmenopausal women (Ryan et al., 2002, Green et al., 2004, Christiansen et al., 2009, Visseres et al., 2013) and ovariectomized rats (Barros et al., 2006, Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010) receiving HRT has been reported before. Insulin and glucose decrease omentin mRNA expression and secretion in omental adipose tissue explants (Batista et al., 2007, Moreno-Navarrete et al., 2010, Yang et al., 2006, Yu and Gong, 2011). In line with our study, there are some other studies (Moreno-Navarrete, 2010) reporting a positive correlation between omentin-1 level and insulin sensitivity. Similarly in the absence of estrogen, there is a reduction in insulin-stimulated translocation of GLUT4 to the plasma membrane as well as a reduction in muscle glycogen synthase expression, which leads to insulin resistance. The fact that omentin enhances only insulin-mediated glucose transport without affecting on

basal glucose transport, indicates that omentin-1 has no intrinsic insulin-mimic activity (Fu et al., 2004). Generally, based on our data increase in omentin-1 level correlates with improving insulin sensitivity; thus the significant reduction in insulin resistance by Exe, Est and Exe+Est in the present study probably relates to the glucose intake and GLUT4 translocation mediated by omentin-1. The reduction in visceral fat with no significant changes in body weight probably reflects either reduction of total fat mass (Dieli-conwright et al., 2010), or increase in another component of the body (e.g. muscles, bone mass) (Dieli-conwright et al., 2010, Evans et al., 2001). The intensity of training in the present study was adequate to increase in muscle mass and to glucose consumption in skeletal muscle (Aguar et al., 2010) and also up regulation of insulin receptors by omentin-1 (Yang et al., 2006).

Interestingly in the present study, despite the increasing food intake in Exe group, visceral fat and insulin resistance were reduced. Increasing food intake might be due to enhanced energy metabolism (Visseres et al., 2013) by omentin (Yu and Gong,

2011), which takes place via activating AMPK signaling (AMP-activated protein kinase) in Muscle (Yu and Gong, 2011). Free fatty acid is a major risk factor for insulin resistance and ectopic fat storage in muscle (Yang et al., 2006) via decreasing glucose transport (Yu and Gong, 2011). Exercise increased insulin sensitivity in part by stimulating AMPK (Malin et al., 2012) and consequently increase in glucose intake (Malin et al., 2012).

Another mechanism for a preferential reduction of Visceral fat by exercise might be through increase in the level of catecholamines and further lipolysis (Christiansen et al., 2009), or cortisol (Christiansen et al., 2009).

On the other hand, lack of estrogen increased body weight, partially by increasing visceral fat, which was reported in our (Babaei et al., 2010, Damirchi et al., 2010), and also previous studies (Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010, Toth et al., 2000). One possible explanation might be enhancement of adipocytes and reduction in lipase activity in OVX animals (Babaei et al., 2010, Saengsirisuwan et al., 2009, Zoth et al., 2012, Zoth et al., 2010).

Finally a combination of aerobic-resistance training and estrogen replacement therapy was more effective than aerobic-resistance training or estrogen replacement therapy alone in attenuating visceral fat and insulin resistance. We can assume that resistant training probably lead to skeletal muscle growth and decrease in adiposity (Urbanova et al., 2014) and aerobic training resulted in significant reductions in visceral fat and abdominal subcutaneous fat (Slentz et al., 2011). Our results are in agreement with Zoth and colleagues (2012) and Evanz and colleagues (2001), but not with Saengsirisuwan and colleagues (2009) and Green and colleagues (2004). The inconsistency might be due to difference in laboratory methods, hormone replacement regimens and training protocols.

To our knowledge, this is the first study investigating the effects of aerobic-resistance training and estrogen replacement therapy, independently and combined, on visceral fat, insulin resistance, lipid profile and omentin-1 level in the hypoestrogenism status. We conclude that although aerobic-resistance training, estrogen replacement therapy, and combination of these two are

effective strategies in targeting visceral fat accumulation and insulin resistance in an animal model of menopause, it seems exercise per se is more effective/ constructive. Moreover, elevation in omentin following our treatment possibly reflects a physiological compensatory mechanism to target metabolic syndrome.

Therefore, from the clinical point of view, this study suggests that aerobic-resistance training is a positive strategy/way to combat metabolic syndrome probably via increasing omentin.

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Conflict of interest

The authors declare that they have no conflict of interest.

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