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Six months training alone or combined with diet alters HOMA-AD, HOMA-IR and plasma and adipose tissue adiponectin in obese women

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Abstract

OBJECTIVE: We investigate the effect of 6 months aerobic training alone or in combination with diet on adiponectin in circulation and in adipose abdominal tissue (AT) in obese women.
METHODS: Twenty obese subjects were randomized into a 24 weeks intervention: 1) training (TR) and 2) training and diet (TRD). Blood samples were collected at baseline, after 12 wk and 24 wk. AT biopsies were obtained only at baseline and after 24 wk.
RESULTS: In the TRD group the fat loss was after 12 wk –13.74% ($p<0.01$) and after 24 wk –21.82% ($p<0.01$) with no changes in the TR group. After 12 and 24 wk, VO_{2max} was increased by 21.81–39.54% ($p<0.05$) in the TRD group and 18.09–40.95% in the TR group ($p<0.05$). After 12 wk, plasma adiponectin was raised only in the TRD group (55.8%, $p<0.05$). After 24 weeks, circulating adiponectin was elevated by 110.4% ($p<0.01$) in the TRD group and by 27% ($p<0.05$) in the TR group. In AT biopsies, subjects in the TRD and TR groups exhibited a significant increase in adiponectin ($p<0.05$ and $p<0.01$, respectively). The two indices HOMA-IR and HOMA-AD for assessing insulin resistance were strongly affected by protocols. HOMA-IR decreased ($p<0.05$) only after 24 wk in the TRD group. HOMA-AD increased in both groups after 12 ($p<0.05$) and 24 wk ($p<0.01$).
CONCLUSION: Six months chronic aerobic exercise alone or combined with diet result in a significant increase in circulating and adipose tissue adiponectin levels in obese women independent of changes in body composition and/or in HOMA-IR.

ORIGINAL ARTICLE

INTRODUCTION

Obesity and related metabolic disorders are among the most important public-health concerns in developed nations (Jia & Lubetkin 2010). Human adipose tissue is recognized as having an endocrine function in combination with its role in energy metabolism and storage (Daval *et al.* 2006). Adiponectin is a protein secreted primarily by adipose tissue, and its targets include the liver and skeletal muscle where, among other functions, it regulates energy metabolism and insulin sensitivity (Lafontan *et al.* 2006; Wang *et al.* 2006). Exercise training is a useful therapy for improving insulin sensitivity and cardiovascular disease. Several studies exploring the effects of exercise on circulating adiponectin levels have resulted inconsistent findings (Bouassida *et al.* 2010). Aerobic training improves insulin sensitivity, body composition, lipoprotein profile, and metabolic and cardiovascular health can affect adiponectin concentrations (Das 2004). Several studies reported that chronic exercise increases (Markofski *et al.* 2014; Racil *et al.* 2013; Shing *et al.* 2013) or does not increase (Asad *et al.* 2012) adiponectin levels.

In general, studies employing short-term (<12 weeks) training protocols showed non-significant changes in adiponectin. Indeed, eight weeks endurance training or resistance training in sedentary students (Asad *et al.* 2012) or in obese men (Hara *et al.* 2005) do not affect adiponectin concentrations. Long-term (≥12 weeks) exercise studies that affect body composition or insulin resistance are commonly accompanied by increased adiponectin concentrations (Moghadasi *et al.* 2012; Racil *et al.* 2013). Christiansen *et al.* (2010) indicated that diet-induced weight loss, exercise independently and in combination enhances the adiponectin concentrations in AT but only a pronounced hypocaloric induced weight-loss increases circulating adiponectin in obese subjects.

Insulin resistance (IR) is evaluated by the homeostasis model assessment for insulin resistance (HOMA-IR), a surrogate of the hyperinsulinemic euglycemic clamp, which is considered the standard method in IR determination (Matthews *et al.* 1985). HOMA-AD was recently described for assessing IR and was more accurate than HOMA-IR, especially in patients with higher BMI (Matsuhisa *et al.* 2007). To our knowledge, the HOMA-AD index has never been tested before and after aerobic training in obese women

The aim of the present study was to investigate the independent effect of 6 months aerobic training alone or in combination with diet on i) adiponectin concentrations in circulation and in AT and on ii) HOMA-IR and HOMA-AD in obese subjects to determine whether exercise training per se, independent or in combination with diet would affect these parameters. We hypothesized that both interventions would increase adiponectin in circulation and in AT and decrease insulin resistance in obese women.

METHODS

Subjects

Twenty obese healthy females participated in this study. Obesity was defined as a body mass index (BMI; kg/m^2) between 30 and 40 kg/m^2. Exclusion criteria were cardiovascular disease, type 2 diabetes, pregnancy, or orthopaedic difficulties causing inability to undertake an exercise program. No subjects received medication that could affect the investigated metabolic markers. Prior to participation, the subjects gave a written informed consent. This study was approved by the local ethics committee of the Faculty of medicine, university of Sousse, Tunisia. The women gave a written informed consent for the experimental protocol. The 20 obese women were randomized into the 24 weeks intervention study consisting of 1) training alone (TR) and 2) hypocaloric diet plus training (TRD).

Anthropometric measurements

Height was measured with a standing stadiometer and recorded with a precision of 0.1 cm. Waist circumference was taken as the smallest circumference between the lower costal margin and the pelvic brim measured to the nearest 0.5 cm. Body mass (measured to the nearest 0.1 kg), fat free mass and percent body fat were measured using bioelectrical impedance analysis (BEURER, Germany). Participants were nude or wearing only underwear for measurements of body mass. Body mass index (BMI) was calculated using the standard formula: body mass in kilograms divided by height in meters squared (kg/m^2).

Exercise stress test

Participants performed an incremental exercise test to exhaustion on a calibrated cycle ergometer (Ergoline, Germany) to determine maximal oxygen consumption (VO_{2max}). The test consisted in a 5 min warm-up followed by increments in power of one minute at 60 rpm until exhaustion. The loads during warm-up and increments were individually adjusted by taking into account the age, height and body mass of each subject (Wasserman *et al.* 1987). The analyzer was calibrated before the rest with the gases of known concentration. Validation of attainment of VO_{2max} satisfied two of the following four criteria: 1) an oxygen uptake plateau despite increasing exercise intensity, 2) respiratory exchange ratio ≥1.10, 3) maximal heart rate within 10 beats/min of the age predicted maximal values (Tanaka *et al.* 2001) and 4) subject exhaustion.

Training intervention

Aerobic training included three sessions per week of walking/running on a treadmill, starting at 55% of maximal heart rate for 30 min for weeks 1–4 for 30 min. Exercise intensity and duration were gradually increased every month until subjects exercised at 80% of maximum heart rate for 45 min at weeks 20–24.

Training and diet intervention

The TRD intervention combined the above intervention with hypocaloric diet as follow: A balanced and personalized dietary restriction program was established by a dietician after an initial dietary assessment in order to define the total amount of calories consumed per day. Subjects in TRD group recorded the times and amounts of food and fluid intake for a week before the beginning of the program. The dietary program was set at −500 kcal/day below the initial dietary records. It was composed of 15% proteins, 55% carbohydrates and 30% lipids. The women recorded, in a specifically designed notebook, the quantity of food and the time at which it was eaten (4 times a week). The foods were selected according to the subject's dietary habits. Power Point presentations, videos and role-play scripts were designed for trainers to use during the educational program. Each individual's diet was designed using a Bilnut 4 Software package (SCDA Nutrsoft, Cerelles, France), a computerized database that calculates the food intake and composition from the National Institute of Statistics of Tunis 1978. The body mass was measured every week to assess the immediate effect of the nutritional modifications.

Blood sampling and analysis

Blood samples were collected by venepuncture on 3 occasions: at the beginning of the protocol control value (CV), after 12 weeks (S1) and after 24 weeks (S2). Blood samples were collected in the morning at 7 to 8 am after an overnight fast. The plasma was separated and frozen at −80 °C for later analysis. Fasting plasma and adipose tissue adiponectin concentrations were measured by immunoradiometric assay (Diagnostic Systems laboratories, USA intra-assay coefficient of variation (CV) was 2.6% and interassay CV was 3.7%). Total cholesterol (TC), triglycerides (TG), and HDL-C levels have been measured using enzymatic methods. The inter-assay coefficients of variation (CV) were of: 1.7, 2.2, and 2.0%, respectively. Fasting plasma glucose concentrations were measured using an automated device (AU2700, Olympus, France). The interassay coefficient of variability (CoV) was 1.7%. Fasting plasma insulin was assayed by an IRMA Insulin kit (Immunotech, France). The intra- and interassay CoV were respectively, 3.3–4% and 3.7–4.8%. Insulin resistance was assessed using the homeostatic model assessment for insulin resistance (HOMA-IR). The HOMA-IR has been validated in obese women and was computed as follows: HOMA-IR : [insulinemia (μU/ml) × glycemia (mmol/l)]/22.5 (Matthews *et al.* 1985). The HOMA-AD index was calculated by the following formula: [insulinemia (μU/ml) × glycemia (mmol/l)]/adiponectinemia (μg/ml) (Matsuhisa *et al.* 2007).

Adipose tissue biopsies

At baseline and after 24 weeks, the AT biopsies were obtained from the abdominal subcutaneous AT depot 5–10 cm lateral to the umbilicus. The skin was anesthetized with lidocaine (10 mg/ml) before a small incision was made, and 200 mg of AT was removed under sterile conditions using a liposuction needle. Immediately after removal, the AT sample was washed in isotonic NaCl, snap-frozen in liquid nitrogen and kept at −80 °C.

Statistical analyses

Data are presented as means ± SD. Statistical analysis was performed using SPSS 12.0 for windows (SPSS Inc., Chicago, IL). A Kolmogorov-Smirnov test was used to determine of normality of distribution of endocrine and metabolic measures which were found to be non-parametric. ANOVA with repeated measures was performed: 2 (protocols) × 2 (groups) × 3 (times). When this analysis revealed significant differences a paired Student t-test was used to identify significant changes between CV to S1 and S2 and a non-paired Student t-test was used to locate where significant differences existed between TR and TRD groups. Correlations between measured parameters were assessed by Spearman's correlation. The level of significance was set at $p<0.05$.

RESULTS

Changes in anthropometric parameters and VO_{2max}

The anthropometric data of the subjects within each group, at the beginning, after 12 weeks and at the end of the program (after 24 weeks), are shown in Table 1.

Subjects in the TRD group obtained a weight loss of 8.18% (7.36 kg, $p<0.05$) after 12 weeks and of 13.21% (12.36 kg; $p<0.05$) after 24 weeks. This group showes also important fat mass losses of 13.74% (5.36 kg; $p<0.01$) after 12 weeks and of 21.82% (8.51 kg; $p<0.01$) after 24 weeks. In addition, in TRD group 12 and 24 weeks provoked a loss in waist circumferences of 2–6 cm ($p<0.01$). In the TRD group, BMI was significantly reduced after 12 ($p<0.05$) and 24 weeks ($p<0.01$), there were no changes in the TR group. In both groups, free fat mass showed small increases after 12 and 24 weeks but these increases were not significant. Participants in the TRD and TR groups increased their VO_{2max} with 21 and 18%, respectively after 12 weeks ($p<0.05$) and with 39 and 41% respectively after 24 weeks ($p<0.05$) (Figure 1).

Changes in metabolic and hormonal parameters

The absolute values of the metabolic and metabolic parameters are presented in Table 2. Only in the TRD group glucose, insulin, and HOMA-IR were reduced after 24 weeks with 12% ($p<0.01$), 39% ($p<0.05$) and 45% ($p<0.05$), respectively. While there were no significant changes in the TR group. HOMA-AD increased in the TRD and TR groups after 12 weeks with 7–16.5% ($p<0.05$), respectively and after 24 weeks with 27–76% ($p<0.01$), respectively (Table 2).

After 12 weeks, plasma adiponectin was raised only in the TRD group (55.8%, $p<0.05$). After 24 weeks, cir-

Tab. 1. The characteristics of the subjects before, after 12 and 24 weeks.

	TRD (n=10)			TR (n=10)		
	Before (CV)	After 12 weeks (S1)	After 24 weeks (S2)	Before (CV)	After 12 weeks (S1)	After 24 weeks (S2)
Age (Years)		38.90±4.37			36.20±5.00	
Height (m)		1.68±0.03			1.61±0.05	
Waist circumference (cm)	99±5	97±4	93±5*	98±5	98±5	97±5#
Weight (kg)	92.46±5.5	85.10±5.26*	80.30±5.06*	86.99±7.96	85.00±7.52	82.80±7.52
BMI (kg/m^2)	32.98±2.17	30.36±2.08*	28.65±2.07**	33.52±3.75	32.76±3.61	31.92±3.69
Body Fat (%)	42±1.49	39.76±1.28**	38.26±0.84**	41.26±1.22	41.24±1.23#	41.12±1.35#
Body fat mass (kg)	39.26±3.50	33.90±3.08**	30.75±2.47**	35.96±4.19	35.13±4.05	34.13±4.10#
Fat free mass (kg)	25.29±0.57	26.80±0.46	27.16±0.38	24.97±0.99	25.39±1.02	26.79±1.16
$VO_{2\ max}$ (ml/min/kg)	22.30±2.97	27.10±1.92*	31.00±2.02*a	21.30±1.42*	25.10±1.22*	29.90±1.14*

Data are presented as means ± SD. TRD: Training and diet combined; TR: Training only; BMI: Body Mass Index; CV: Control Value; S: Sampling. *p<0.05; **p<0.01 CV *vs* S1 and S2. #p<0.05 TRD *vs* TR.

Tab. 2. Changes in metabolic and inflammatory parameters before, after 12 and 24 weeks.

	TRD (n=10)			TR (n=10)		
	Before (CV)	After 12 weeks (S1)	After 24 weeks (S2)	Before (CV)	After 12 weeks (S1)	After 24 weeks (S2)
Glucose (mmol/l)	4.94±0.43	4.83±0.37	4.35±0.40**	4.95±0.44	4.8±0.54	4.62±0.29
Insulin (µU/ml)	15.34±6.37	12.63±7.45	9.53*±3.65	9.48±3.95	9.02±5.31	7.97±4.39
HOMA-IR	3.32±1.34	2.69±1.64	1.84±0.68*	2.07±0.86	1.90±1.06	1.95±0.98
HOMA-AD	1.74±0.44	1.86±0.54*	2.21±0.50**	1.64±0.44	1.96±0.54*	2.89±0.50**
Total cholesterol (mmol/l)	4.98±0.90	4.43±0.41*	3.89±0.30**	4.79±1.25	4.40±1.09*	3.92±0.20**
HDL-cholesterol (mmol/l)	0.95±0.07	1.10±0.09**	1.26±0.15**	0.91±0.20	0.99±0.22*	1.06±0.26**
Triglyceride (mmol/l)	1.46±0.21	1.22±0.18*	0.89±0.14**	1.33±0.42	1.18±0.31*	0.98±0.33**
Adiponectin in plasma (pg/ml)	1.72±0.57	2.70±0.57*	3.62±1.08**	1.74±0.44	1.76±0.54	2.21±0.50*
Adiponectin in AT (pg/ml)	1.90±0.26		3.39±0.66**	1.57±0.30		2.28±0.63*

Data are presented as means ± SD. TRD: Training and diet combined; TR: Training only; HOMA-IR: Insulin resistance; CV: Control Value; S: Sampling; AT: Adipose tissue. *p<0.05; **p<0.01 CV *vs* S1 and S2.

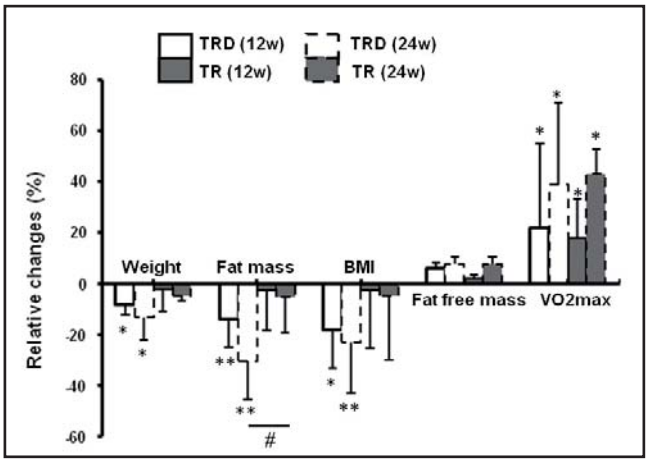

Fig. 1. Changes in weight, fat mass, BMI, free fat mass and maximal oxygen consumption (VO_{2max}) after 12 and 24 weeks in TRD and TR groups. Data are presented as percentage changes in relation to baseline values. TRD: Training and diet combined; TR: Training only. *p<0.05; **p<0.01 *vs* baseline. #p<0.05 TRD vs TR.

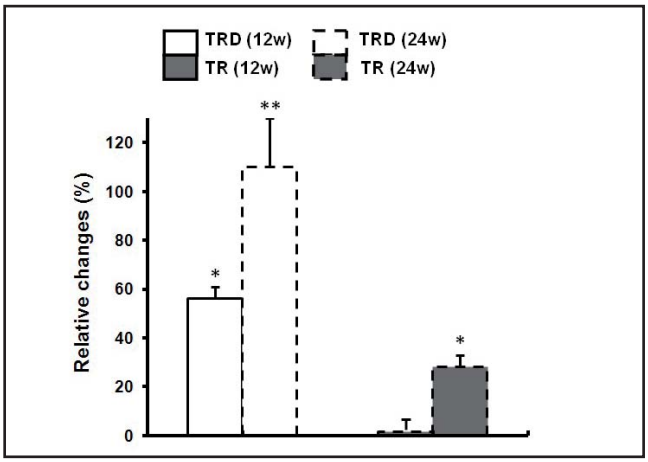

Fig. 2. Relative changes in serum levels of adiponectin after 12 and 24 weeks in TRD and TR groups. Data are presented as percentage changes in relation to baseline values. TRD: Training and diet combined; TR: Training only. *p<0.05; **p<0.01 *vs* baseline.

culating adiponectin was elevated by 110.4% (p<0.01) in the TRD group and by 27% (p<0.05) in the TR group (Figure 2). In adipose tissue, adiponectin was significantly increased by about 78% (p<0.01) in the TRD group and by 45% (p<0.05) for TR group (Figure 3). Lipid profile was strongly affected by the two interventions. Total cholesterol and triglycerides were reduced similarly in the two groups after 12 weeks (p<0.05 for all) and after 24 weeks (p<0.01 for all). HDL cholesterol was significantly increased in boyh groups after 12 and 24 weeks (p<0.05 and p<0.01) (Figure 4).

Correlations

Our results showed only significant correlations between plasmatic and adipose tissue adiponectin in TRD and TR groups. In these two groups, at baseline and after 24 weeks, plasmatic adiponectin was significantly related to adiponectin in AD (r=0.875, p<0.01) and (r=0.860, p<0.01), respectively.

DISCUSSION

The present findings support our first hypotheses and suggest that six months aerobic exercise alone or combined with diet results in a significant increase in plasma and adipose adiponectin levels in obese women. Our results are so controversial because we noted increased adiponectin in circulation and in plasma after six months aerobic training with no significant changes in body composition. It is worth noting that the increases in adiponectin observed in the present study occurred in the absence of any changes in weight or waist circumference. As such, these findings add to the growing body of evidence showing that training results in important health benefits irrespective of changes in body weight (Thompson *et al.* 2001; Duncan *et al.* 2003).

It has been suggested that a weight loss of at least 10% is needed to increase systemic levels of adiponectin (Madsen *et al.* 2008). Indeed, a majority of studies suggest that weight loss produced by training may be the driving mechanism for increases in adiponectin (Kobayashi *et al.* 2006; Polak *et al.* 2006). There are negative relationships between plasma adiponectin levels and weight (Guebre-Egziabher *et al.* 2005; Ryan *et al.* 2003) and body mass index (Guebre-Egziabher *et al.* 2005). In this context, i) Racil *et al.* (2013) showed that 12 weeks high intensity interval training and moderate interval training decreased percent body fat and increased adiponectin concentrations by respectively 6.3 and 16.2% in obese young females, ii) Shing *et al.* (2013) demonstrated that 4 weeks of high-intensity interval training is associated with an increase in adiponectin concentrations and a reduction in body fat in rowers and iii) Mogadasi *et al.* (2012) noted that 12 weeks high-intensity exercise training caused an increase in adiponectin concentrations and a decrease in BMI as well in central and peripheral adipose tissue. Conversely, Mediano *et al.* (2013) demonstrated that small-volume, home-based exercise for 12 months did not change adiponectin concentrations but decreases weight in non-obese women. On the other hand, 8 weeks of endurance, resistance or concurrent training don't affect significantly adiponectin concentrations and body composition (Asad *et al.* 2012). Like our results, despite no significant changes in body composition, Mujander *et al.* (2011) and Markovski *et al.* (2013) noted respectively significant increases in circulating adiponectin (30%) following 6 months aerobic training in untrained males and (55%) after 12 weeks of combined aerobic and resistance exercise training in older adults.

In the present study, there was a similar increase after 24 weeks training in adiponectin in circulation and in adipose tissue. We speculate that the rate of adi-

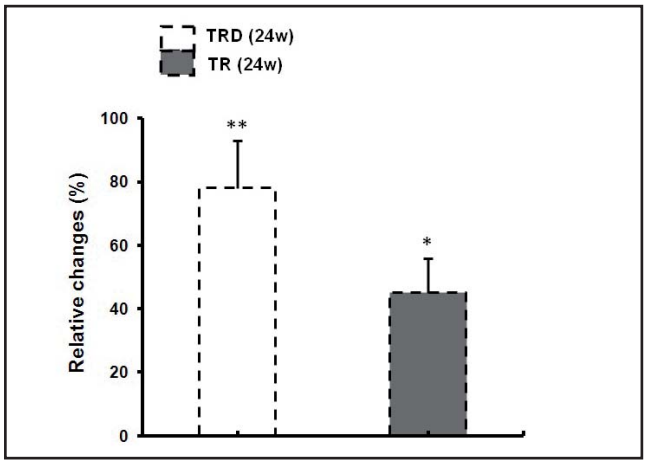

Fig. 3. Relative changes in adipose tissue levels of adiponectin after 12 and 24 weeks in TRD and TR groups. Data are presented as percentage changes in relation to baseline values. TRD: Training and diet combined; TR: Training only. *p<0.05; **p<0.01 *vs* baseline.

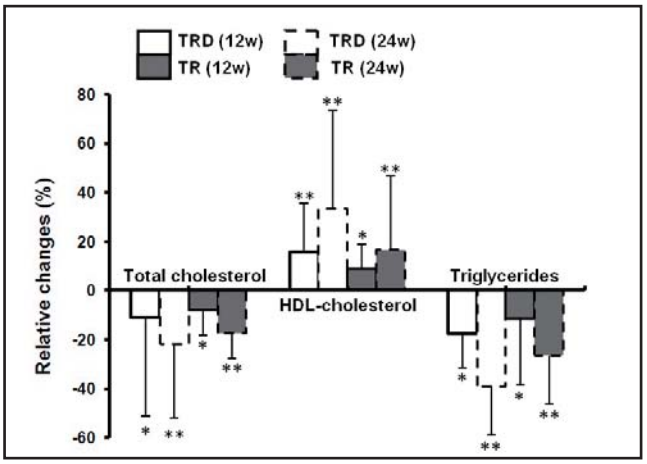

Fig. 4. Relative changes in serum levels of total cholesterol, HDL-cholesterol and triglyceride after 12 and 24 weeks in TRD and TR groups. Data are presented as percentage changes in relation to baseline values. TRD: Training and diet combined; TR: Training only. *p<0.05; **p<0.01 *vs* baseline.

ponectin secretion from adipose tissue into the circulation was unaffected and could explain the same values in circulation. The correlation between both changes in adipose tissue and circulating levels of this hormone is therefore comprehensible. In this context, Christiansen *et al.* (2010) demonstrated an increase in adiponectin in subcutaneous adipose tissue and in circulation after 12 weeks of aerobic training in obese males and females.

Potential mechanisms

Although insulin levels and HOMA-IR have been suggested to play a role in acute changes in adiponectin levels (Jürimäe *et al.* 2005; Racil *et al.* 2013), it seem unlikely to explain the increase in adiponectin in circulation and in AT observed in the present study. In the present study, adiponectin levels were elevated in both protocols while insulin levels and HOMA-IR were reduced only after 12 and 24 weeks during the training combined with diet. This suggests that changes in insulin levels and HOMA-IR are not the primary mediators of the observed change in adiponectin levels. An alternative explanation for weight loss–independent changes in adiponectin may be related to the small but insignificant increases in fat free mass noted after 12 and 24 weeks training alone or combined with diet. Changes in fat free mass influence metabolic activity and overall energy balance (Fatouros *et al.* 2005), and it is possible that a statistically insignificant increase in fat free mass has metabolic consequences. Recent research has linked exercise and muscle gains in elderly people to a decrease in muscle inflammatory gene expression (Lambert *et al.* 2008). Nevertheless, these positive changes associated with exercise, despite no change in body weight, underscore the importance of including exercise for a healthy lifestyle.

Reported correlations between changes in insulin resistance and changes in adiponectin have been inconsistent. Some have shown that adiponectin increases with improved insulin sensitivity (Racil *et al.* 2013); others have shown that adiponectin increases without improvement in insulin sensitivity (Mujumdar *et al.* 2011); and still others have shown no change in adiponectin despite improved insulin sensitivity (Ahmadized *et al.* 2007). In our 6 months study, significant increases in circulating and adipose tissue adiponectin levels occurred in TRD and TR groups without corresponding reductions in HOMA-IR in TR group. Our findings suggest that exercise-induced increases in adiponectin in obese females occur without changes in insulin sensitivity. The mechanisms responsible for the increase in insulin sensitivity after chronic exercise are not entirely clear. Depletion of muscle glycogen leads to enhanced insulin-mediated glucose uptake in the previously exercised muscles to facilitate glycogen replenishment (Holloszy 2005). Intramuscular triglyceride is also closely associated with insulin sensitivity (Goodpaster & Brown 2005), and depletion of skeletal muscle lipid stores during exercise in conjunction with enhanced lipid oxidation after exercise could also facilitate muscle insulin action (Bruce & Hawley 2004).

Our study demonstrated that lipidic profile was altered after aerobic training alone or combined with hypocaloric diet in obese women. It is generally considered that aerobic exercising has several beneficial effects on health. For example, regular exercise may promote chronic positive effects such as an improvement in lipid profiles, insulin resistance, BMI and percent body fat, as well as basal metabolic state (Sharma 2003). As the metabolism of lipoproteins occurs mainly during the aerobic exercise (Kelley & Kelley 2008), the positive changes or the stability in anthropometric variables observed in the present study indicate that aerobic exercising has the potential to improve the lipid profile.

The strengths of this study include robust measures because we have not only measure the level of the concentrations of adiponectin in circulation but also in abdominal adipose tissue. As mentioned previously, the present study focused only on adiponectin concentrations, rather than looking at concentrations of specific hormones that can modulate adiponectin concentrations such as leptin, interleukin-6 and tumor necrosis factor (Chen *et al.* 2011; Christiansen *et al.* 2010). The current study also fixed exclusively on an obese women group, and thus our findings may not translate to other individuals with ages or phenotypes different from those of participants in the current sample. Additionally studies on men, normal weight or trained individuals, children and diabetic subjects would be of interest.

In conclusion, we report that six months chronic aerobic exercise alone or in combination with hypocaloric diet result in a significant increase in circulating and adipose tissue adiponectin levels in obese women independent of changes in body composition and/or in HOMA-IR.

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Conflict of interest

The authors declare that they have no conflict of interest related to the publication of this article.

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