

Resistance Training Improves Cardiovascular Risk Factors in Obese Women Despite a Significant Decrease in Serum Adiponectin Levels

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Increased circulating adiponectin and insulin sensitivity are usually observed after body fat loss induced by a weight-loss diet. Progressive resistance training (PRT) without a concomitant weight-loss diet significantly decreases visceral fat, thus improving insulin sensitivity. Therefore, the purpose of this study was to ascertain the effects of combined 16-week PRT and weight-loss diet on circulating adiponectin and insulin sensitivity index. Thirty-four obese (BMI: 30–40 kg/m²) women, aged 40–60 year, were randomized to three groups: a control group (C; *n* = 9); a diet group (WL; *n* = 12) with a caloric restriction of 500 kcal/d; and a diet plus resistance training group (WL+RT; *n* = 13) with the same caloric restriction as group WL and a 16-week supervised whole body PRT of two sessions/week. Both WL and WL+RT groups showed similar decreases in body mass (−6.3% and −7.7%) and visceral fat (−19.9% and −20.5%). WL resulted in an expected increase in circulating levels of adiponectin (*P* = 0.07) and insulin sensitivity. However, circulating total adiponectin decreased (*P* < 0.05) in WL+RT group, whereas an improvement in different cardiovascular risk factors (insulin sensitivity, low-density lipoprotein cholesterol (LDL-C), etc.) was observed. In conclusion, in obese women a 16-week combined PRT and weight-loss diet is accompanied by significant improvements in different cardiovascular risk factors in spite of a significant decrease of circulating adiponectin.

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INTRODUCTION

At present, adiponectin may be the most important and promising adipocytokine for obtaining a better understanding of the link between obesity and metabolic and cardiovascular disease (1,2). Recent studies have revealed that this adipocytokine exhibits antidiabetic (3), anti-inflammatory, and antiatherogenic properties (4). Adiponectin has been shown to be secreted principally by visceral adipose tissue (VAT), the size of this visceral fat depot being an important correlate of plasma adiponectin levels (5). Moreover, it is known that an excess of abdominal adipose tissue is a better predictor of the development of insulin resistance, type 2 diabetes and cardiovascular disease than the total amount of adipose tissue (6,7). Circulating levels of adiponectin may be the link between visceral obesity and certain related metabolic abnormalities which contribute to the development of insulin resistance, type 2 diabetes and atherosclerosis (3,8,9).

Lifestyle changes such as weight loss and regular physical activity are recognized as effective nonpharmacological interventions with beneficial effects on metabolic and cardiovascular risk factors (6,10). In this context, different studies have demonstrated that, without a concomitant weight-loss diet, progressive resistance training (PRT) significantly decreases visceral fat in older men (11) and women (12), improving insulin sensitivity (11). However, at present both the effect of PRT on circulating adiponectin and the physiological role of adiponectin on the improvement of metabolic and cardiovascular risk factors with either body or fat mass loss are as yet incompletely understood (1,13).

In the present study, we hypothesized that a twice-weekly PRT would be particularly useful in the context of a weight-loss diet in adult obese women, increasing the visceral fat loss usually observed with a hypocaloric diet in women (14).

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This could yield highly favorable changes in circulating adiponectin and, as a result, to the metabolic and cardiovascular risk.

METHODS AND PROCEDURES

Subjects

Thirty-four sedentary, nonsmoking, obese (BMI: 30–40 kg/m²) women, aged 40–60 years, were recruited through an advertisement in a local newspaper. Before inclusion in the study, all candidates were thoroughly screened using an extensive medical history, resting and maximal exercise electrocardiogram and blood pressure measurements. Cardiovascular, neuromuscular, arthritic, pulmonary, or other debilitating diseases as determined by one or all of the screening tools were reasons for exclusion from the study. None of the subjects received any medication. All the subjects were informed in detail about the possible risks and benefits of the project, and they then signed a written consent form before participating in the study. This project was approved by the ethical committee of the regional Health Department. Participants were randomized to three groups: a control group (C; *n* = 9); a diet group (WL; *n* = 12) with a caloric restriction of 500 kcal/day; and a diet plus resistance training group (WL+RT; *n* = 13) with the same caloric restriction as group WL and a 16-week supervised whole-body resistance training program of two sessions/week. Perimenopausal women were balanced among groups. The subjects were tested on two different occasions (weeks 0 and 16) using identical protocols. During the 16 weeks of the study the subjects maintained their customary recreational physical activities (e.g., walking). The baseline characteristics of the subjects are presented in [Table 1](#).

Anthropometric variables

Height of the barefoot subjects was measured to the nearest 0.1 cm. Body mass was measured on the same standard medical scale to an accuracy of ± 100 g. Waist and hip circumferences were measured with the subject standing erect with arms at the sides and feet together, wearing only underwear. The measurer placed an inelastic tape around the subject, without compressing the skin, on a horizontal plane at the level of the last false rib and the buttocks, respectively. The measurement was recorded to the nearest 0.1 cm.

Magnetic resonance

The volumes of visceral and subcutaneous adipose tissue (SAT) (abdominal and thigh) and muscle volume in the thigh were measured by magnetic resonance (MR). MR imaging was performed with a 1T magnet (Magnetom Impact Expert; Siemens, Erlangen, Germany) using body coil ([Figure 1](#)). The subjects were examined in a supine position with both arms positioned parallel along the sides of the body. We obtained a spoiled T1-weighted gradient-echo sequence with repetition time = 127 ms and echo time = 6 ms. Each half body volume was scanned using two stacks, each containing 10 contiguous 10 mm thick slices. Each stack was acquired in 20 s and interleaved slice order was used. A field of view of 500 mm was used and all the stacks were acquired with breath-holding. The total investigation time was about 5 min.

MR imaging of both thighs was then obtained. T1-weighted sequence was used with a repetition time of 645 min and a spin echo time of 20 min. The field of view was 500 × 500 mm and the matrix was 512 × 192. The slices were 10 mm thick, with no gap between the slices. The thighs were scanned using two stacks, each containing 15 contiguous 10 mm thick slices; the scan was performed axially from the articular boundary

Table 1 Selected anthropometric, muscle strength, and energy intake and expenditure variables, before and after the 16 weeks of the intervention (week 0 and week 16)

| | Control group (<i>n</i> = 9) | | WL group (<i>n</i> = 12) | | WL+RT group (<i>n</i> = 13) | |
|--------------------------------------|-------------------------------|-----------------|---------------------------|--------------------|------------------------------|--------------------|
| | Week 0 | Week 16 | Week 0 | Week 16 | Week 0 | Week 16 |
| Age | 50.2 ± 6.8 | | 51.4 ± 5.5 | | 48.6 ± 6.4 | |
| Anthropometric | | | | | | |
| Body weight (kg) | 88.9 ± 11.4 | 88.8 ± 10.5 | 88.0 ± 15.2 | 82.3 ± 14** | 90.2 ± 12.7 | 83.1 ± 10.9*** |
| BMI (kg/m ²) | 35 ± 3.6 | 35 ± 3.3 | 34.6 ± 3.4 | 32.4 ± 3.7*** | 35 ± 3.1 | 32.3 ± 3*** |
| Waist (cm) | 100 ± 7.4 | 99.9 ± 8 | 101.1 ± 6.5 | 94.5 ± 9.9*** | 99.7 ± 8.3 | 93.4 ± 8.8*** |
| WHR | 0.9 ± 0.05 | 0.9 ± 0.03 | 0.9 ± 0.03 | 0.9 ± 0.02** | 0.9 ± 0.03 | 0.9 ± 0.02** |
| Abdominal | | | | | | |
| Subcutaneous fat (cc) | 14,197 ± 3,320 | 14,053 ± 3,077 | 13,819 ± 3,278 | 11,832 ± 3,326*** | 15,307 ± 2,970 | 11,954 ± 2,446*** |
| Visceral fat (cc) | 3,175 ± 1,122 | 3,157 ± 1,073 | 3,340 ± 977 | 2,724 ± 1,052*** | 3,290 ± 1,141 | 2,633 ± 1,000*** |
| Thigh | | | | | | |
| Subcutaneous fat (cc) | 95,799 ± 20,304 | 96,645 ± 20,310 | 84,886 ± 23,867 | 73,085 ± 20,427*** | 10,3912 ± 16,407 | 87,520 ± 13,826*** |
| Muscle (cc) | 45,452 ± 6,760 | 45,137 ± 6,429 | 47,725 ± 9,141 | 46,244 ± 9,420* | 47,819 ± 9,015 | 47,455 ± 8,961 |
| Energy intake (kcal/d) | | | | | | |
| Carbohydrates (g/d) | 1,864 ± 382 | 1,709 ± 154 | 1,863 ± 440 | 1,598 ± 541* | 1,756 ± 370 | 1,429 ± 223** |
| Protein (g/d) | 79.7 ± 17.5 | 82 ± 20.5 | 86.6 ± 24 | 81.1 ± 31.3 | 83.4 ± 16.8 | 81 ± 10.8 |
| Fat (g/d) | 89.3 ± 17.6 | 78.3 ± 13.3 | 92.4 ± 25.8 | 68.6 ± 28.7** | 92.1 ± 18.3 | 56.7 ± 16.1*** |
| Habitual energy expenditure (Kcal/d) | 2,436 ± 257 | 2,438 ± 245 | 2,357 ± 443 | 2,437 ± 482 | 2,376 ± 339 | 2,331 ± 337 |
| Muscle strength | | | | | | |
| 1-RM bench-press (kg) | 31.7 ± 7.8 | 32.1 ± 7.9 | 29.6 ± 4.5 | 28.9 ± 5.1 | 32.9 ± 6.7 | 44.4 ± 7.7***,† |
| 1-RM half-squat (kg) | 179.6 ± 33.5 | 182.3 ± 33.4 | 184.0 ± 34 | 200.3 ± 55.2 | 183.3 ± 40.1 | 291 ± 73.4***,† |

Values are expressed as means ± s.d.

P* < 0.05, *P* < 0.01, ****P* < 0.001 between values in weeks 0 and 16. Differences between groups after intervention: †*P* < 0.001 between C–WL+RT and WL–WL+RT.

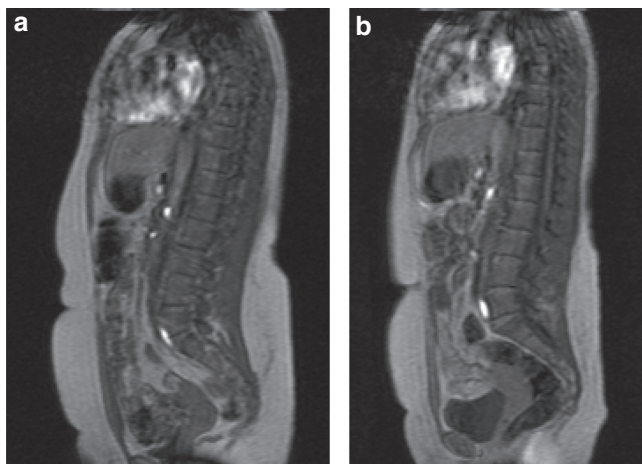


Figure 1 Magnetic Resonance of an obese woman's trunk (a) before and (b) after a 16-week combined progressive resistance training and weight-loss diet.

of the lowest external femoral condyle. The images were retrieved from the scanner according to a DICOM (Digital Imaging and Communications in Medicine) protocol. The acquired axial MR images were transferred to an external personal computer running Windows XP. The level of each abdominal image was labeled using sagittal scout images, referred to the discal level. We used specially designed image analysis software (SliceOmatic 4.3; Tomovision, Montreal, Quebec, Canada) for quantitative analysis of the images.

Biological variables

Resting blood samples were drawn at weeks 0 and 16. Venous blood samples were obtained at rest between 8:00 and 9:00 AM from the antecubital vein. In premenopausal women, all blood samples were obtained during days 5–9 of the follicular phase to check for possible effects of menstrual phases. Blood was drawn after 12 h of fasting and 1 day of minimal physical activity. The postintervention (week 16) blood draw occurred 72–96 h after the last exercise session. Whole blood was centrifuged at 3,000 rpm for 15 min and the resulting serum was then removed and stored at -80°C until subsequent analysis. Basal glycemia was analyzed using an enzymatic hexokinase method (Roche Diagnostics, Mannheim, Germany). Serum insulin levels were measured in duplicate by monoclonal immunoradiometric assay (INSI-CTK Irma; DiaSorin, Madrid, Spain). Intraassay and interassay coefficients of variation were $<5\%$. To estimate insulin resistance, the homeostasis model assessment (HOMA) index was calculated as fasting insulin concentration ($\mu\text{U/ml}$) \times fasting glucose concentration (mmol/l)/22.5. Serum levels of estradiol and progesterone were radioimmunologically measured using commercial kits (Immunotech SAS, Marseille, France) according to the manufacturer's procedures. The intra- and interassay accuracies were 6.2–9.5% and 6.6–10.2% of coefficients of variation for estradiol and 3.5–5.8% and 5.1–9.0% of coefficients of variation for progesterone. Serum adiponectin and leptin levels were measured by commercially available enzyme-linked immunosorbent assay kits (Linco Research, St Charles, MO). The intra- and interassay coefficients of variation were <8 and 7%, respectively. The lowest levels of adiponectin and leptin that can be detected by these assays are 0.78 and 0.50 ng/ml, respectively. No significant cross-reactivity with other cytokines or hormone molecules was detected. Serum triglycerides were measured using Infinity Triglycerides Liquid Stable reagent (ThermoElectron, Noble Park, Australia). High-density lipoprotein cholesterol (HDL-C) concentration was analyzed by a homogeneous method (ITC Diagnostics, Barcelona, Spain). Total cholesterol (TC) concentration was determined in serum according to the IL test cholesterol Trinders method 181618–10 (Instrumentations Laboratory, Lexington, MA). Low-density lipoprotein cholesterol (LDL-C) concentration was

measured by Lipoprint System (Quantimetrix, Redondo Beach, CA). This method is based on electrophoresis of lipid stained serum (Sudan black) in a nondenaturing gel gradient of polyacrylamide. The intra- and interassay coefficients of variation was $<2\%$.

Energy intake and energy expenditure analysis

At weeks 0 and 16 all subjects were interviewed by an experienced dietitian and given instructions on how to complete food records accurately. Three-day dietary food records (including 1 weekend day) were completed, the records being filled out on the actual day of consumption of the foods.

All food records were analyzed by DIETSOURCE (DietSource program; version 1.0; Novartis, Barcelona, Spain).

Similarly, habitual physical activity was evaluated by accelerometry (TriTrac-R3D System, version 2.04; Madison, WI). The TriTrac-R3D was worn on a belt that was firmly attached to the anterior torso of the subject at the level of the waist. TriTrac monitoring was recorded on a minute-by-minute basis over 2 weekdays and 2 weekend days, coinciding with the days of dietary food records.

Hypocaloric diet

Each subject in the WL and WL+RT groups received a varied and well-balanced hypocaloric diet (55% of calories as carbohydrates, 15% as proteins, and the rest as fat) of 500 kcal/day, according to the previous analysis of individual daily energy expenditure by accelerometry. This diet was designed to elicit a 0.5 kg weight loss per week. The control group was asked to maintain body weight. Throughout the 16-week intervention period body weight was recorded once every 2 weeks in both WL and WL+RT groups. Also, every 2 weeks each subject of the intervention groups participated in a series of 1-h seminars in which the dietitian taught proper food selection and preparation, eating behavior, control of portion sizes, and modification of binge eating and other adverse habits.

Strength testing and training protocol

Lower and upper body maximal strength was assessed using 1 repetition concentric maximum (1-RM) action in a half-squat and in a bench-press position, respectively. A detailed description of the 1-RM testing procedure can be found elsewhere (15). In brief, in the half-squat the subjects began the test by lifting a bar in contact with the shoulders with weight plates added to both ends of the bar. On command, the subject performed a concentric extension (as fast as possible) of the leg muscles starting from a knee angle of 90° to reach the full extension of 180° . In the bench-press the bar was positioned 1 cm above the subject's chest and supported by the bottom stops of the measurement device. Maximal strength half-squat was defined as the maximum weight that could be lifted through a full range of motion with proper form. In all tests, strong verbal encouragement was given to each subject to motivate them to perform each test action as maximally and as rapidly as possible. Maximal strength variables showed reliability coefficients ranging from 0.80 to 0.99, and the coefficients of variation ranged from 2 to 7%. Before testing and training, each subject was familiarized with the testing procedure of voluntary force production in several submaximal and maximal actions.

The strength training program used in the present study was similar to that reported previously (15). Briefly, the subjects were asked to report to the training facility twice a week to perform dynamic resistance exercise for 45–60 min per session. A minimum of 2 days elapsed between two consecutive training sessions.

Each training session included two exercises for the leg extensor muscles (bilateral leg press and bilateral knee extension exercises), one exercise for the arm extensor muscle (the bench-press) and four to five exercises for the main muscle groups of the body. Only resistance machines (Technogym, Gambettola, Italy) were used throughout the training period. Resistance in this study was progressively increased or decreased every week for the 16-week training period using a repetition maximum approach, so that the loads that brought about a given relative intensity remained unchanged from week to week.

During the first 8 weeks of the training period the subjects trained with loads of 50–70% of the individual 1-RM, and during the last 8 weeks of the training period the loads were 70–80% of the maximum. In addition, from week 8 to week 16 the subjects performed a part (20%) of the leg extensor and bench-press sets with loads ranging from 30 to 50% of the maximum. In all the individual exercise sessions performed one of the researchers was present to direct and assist each subject towards performing the appropriate work rates and loads. In all subjects average compliance with the diet classes and exercise sessions was above 95%.

Statistical analysis

Standard statistical methods were used for the calculation of the means, standard deviation and Pearson product-moment correlation coefficient. One-way ANOVA was used to determine any differences among the three groups' initial measurements. The resistance training and/or diet related effects were assessed using a two-way ANOVA with repeated measures (groups \times time). When a significant F-value was achieved, Bonferroni *post hoc* procedures were performed to locate the pairwise differences between the means. Selected relative changes were analyzed via one-way ANOVA. Analyses of covariance (ANCOVA) were used to adjust post-interventional values to compare the data between the groups. For this purpose, pre-interventional values were used as covariates so that the effects of the covariance could be observed.

Multiple regression models were used to assess the influence of muscle mass and adipose tissue compartment changes on HOMA index variation and TC changes, taking into account potential factors associated with this variable such as age, changes in BMI, energy intake, fat in diet, adiponectin, leptin, LDL-C, and HDL-C. The models were built in a customized way by the stepwise method. Statistical power calculations for this study ranged from 0.75 to 0.80. The $P < 0.05$ criterion was used for establishing statistical significance.

RESULTS

Subject's characteristics

Baseline characteristics were similar in the three groups (Tables 1 and 2). After 16 weeks, no significant changes were observed in the different parameters evaluated in the control

group. In turn, body mass was significantly diminished after 16 week of intervention in WL and WL+RT groups, by -6.3 and -7.7% , respectively; whereas abdominal SAT decreased by -18.3 and -21.4% ($P < 0.001$) and thigh subcutaneous fat by -16.4% and -18.9% ($P < 0.001$), respectively. Likewise, visceral fat mass was reduced in WL and WL+RT groups by -19.9 and -20.5% ($P < 0.001$), respectively. As expected, in the WL group a significant loss in thigh muscle mass (-5% , $P < 0.05$) was observed; however, thigh muscle mass was maintained in the WL+RT group (Table 1). Finally, by week 16 no significant differences between WL and WL+RT groups were observed, either in body mass or abdominal fat, thigh fat or thigh muscle mass.

Basal relationships between adipocytokines levels and anthropometric and metabolic variables

In the whole group ($n = 34$), no correlation was observed between baseline adiponectin levels and VAT or any other measured fat compartment. Adiponectin correlated negatively with waist-to-hip ratio ($r = -0.359$, $P < 0.05$). In turn, baseline leptin levels correlated with VAT ($r = 0.352$, $P < 0.05$) and with basal insulin and HOMA values ($r = 0.397$, and $r = 0.427$, respectively, $P < 0.05$). Leptin also presented a marked association with BMI ($r = 0.753$, $P < 0.01$), waist ($r = 0.606$, $P < 0.01$), hip ($r = 0.697$, $P < 0.01$), abdominal SAT ($r = 0.720$, $P < 0.01$), and thigh SAT ($r = 0.456$, $P < 0.01$).

Relationships between percentage variations in adipocytokine levels and anthropometric and metabolic variables

In the WL group the difference between baseline and final concentration of adiponectin (Δ adiponectin) was significantly correlated to the concomitant changes in Δ HDL-C ($r = 0.699$,

Table 2 Selected metabolic variables, and lipoprotein profiles before and after the 16-week of the intervention (weeks 0 and 16, respectively)

| | Control group ($n = 9$) | | WL group ($n = 12$) | | WL+RT group ($n = 13$) | |
|---------------------------------------|---------------------------|------------------|-----------------------|--------------------|--------------------------|--------------------|
| | Week 0 | Week 16 | Week 0 | Week 16 | Week 0 | Week 16 |
| Metabolic variables | | | | | | |
| Fasting plasma glucose (mg/dl) | 98.4 \pm 9.8 | 97.4 \pm 7.2 | 100.7 \pm 11.2 | 98 \pm 8.6 | 98.6 \pm 14.9 | 95.8 \pm 13 |
| Insulin (μ U/ml) | 16.8 \pm 5.5 | 13.4 \pm 5.9 | 16.7 \pm 9.2 | 11.4 \pm 7.5** | 15.1 \pm 6.9 | 11 \pm 5.8* |
| HOMA index (10^{-14} / μ U/ml) | 4.2 \pm 1.4 | 2.9 \pm 1.8 | 4.2 \pm 2.4 | 2.8 \pm 2.0** | 3.7 \pm 1.9 | 2.7 \pm 1.7* |
| Leptin (ng/ml) | 34.6 \pm 11.3 | 28.9 \pm 9 | 29.8 \pm 10.4 | 19.8 \pm 10.3*** | 34.8 \pm 10.2 | 20.5 \pm 8*** |
| Adiponectin (μ g/ml) | 12.6 \pm 3.5 | 12 \pm 2.9 | 11.2 \pm 4.3 | 11.9 \pm 3.9 | 13.8 \pm 4.3 | 12.4 \pm 3.5* |
| Estradiol (μ g/ml) | 72.7 \pm 45.2 | 70.3 \pm 37.7 | 114.6 \pm 89.2 | 69.3 \pm 48.9* | 86.9 \pm 73.2 | 67.5 \pm 49 |
| Progesterone (μ g/ml) | 0.7 \pm 1.1 | 0.1 \pm 0.0 | 1.4 \pm 4.2 | 1.7 \pm 4.3 | 1.7 \pm 4.1 | 1.6 \pm 2.9 |
| Lipoprotein profiles | | | | | | |
| Triglycerides (mg/dl) | 140.2 \pm 61.3 | 126.1 \pm 37.5 | 140.8 \pm 48 | 126.3 \pm 44.9 | 111.2 \pm 27.8 | 102.7 \pm 22.8 |
| TC (mg/dl) | 262.6 \pm 35.3 | 249.9 \pm 54 | 250.1 \pm 42.4 | 251.2 \pm 43.6 | 248.6 \pm 33.5 | 214.2 \pm 35.4** |
| LDL (mg/dl) | 155 \pm 29 | 139.4 \pm 44.3 | 147.8 \pm 30.1 | 146.3 \pm 22.8 | 143.3 \pm 27.6 | 122.9 \pm 26.5** |
| HDL (mg/dl) | 64.6 \pm 9.9 | 61.1 \pm 9.5 | 63.7 \pm 14.5 | 64 \pm 9.1 | 69.3 \pm 8.6 | 61 \pm 8.5*** |
| VLDL (mg/dl) | 28.1 \pm 12.4 | 25.3 \pm 7.5 | 28.1 \pm 9.5 | 25.3 \pm 9 | 22.2 \pm 5.4 | 20.6 \pm 4.5 |
| TC/HDL (ratio) | 4.2 \pm 0.8 | 4.1 \pm 0.8 | 4.1 \pm 0.9 | 3.9 \pm 0.4 | 3.6 \pm 0.6 | 3.5 \pm 0.5 |

Values are expressed as means \pm s.d.

HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; TC, total cholesterol; VLDL, very low-density lipoprotein.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ between values before and after the 16 weeks of intervention.

$P < 0.05$). In turn, a marked association was observed between changes in leptin (Δ leptin) and decrease in waist (Δ waist) ($r = 0.749$, $P < 0.01$), hip ($r = 0.734$, $P < 0.01$), thigh subcutaneous fat ($r = 0.757$, $P < 0.01$), abdominal subcutaneous fat ($r = 0.649$, $P < 0.05$), visceral fat ($r = 0.663$, $P < 0.05$), and thigh muscle ($r = 0.592$, $P < 0.05$). In the WL+RT group, by week 16 a negative relation was only observed between Δ adiponectin and concomitant changes in TC (-0.587 , $P < 0.05$). In turn, a marked association was observed between changes in leptin and those observed in body mass ($r = 0.729$, $P < 0.01$), hip ($r = 0.731$, $P < 0.01$), thigh subcutaneous fat ($r = 0.809$, $P < 0.01$), abdominal subcutaneous fat ($r = 0.589$, $P < 0.05$), thigh muscle mass ($r = 0.592$, $P < 0.05$), HOMA value ($r = 0.666$, $P < 0.05$), and basal insulin levels ($r = 0.612$, $P < 0.05$).

DISCUSSION

The main result of this study shows that a whole-body resistance training plus a weight-loss diet in middle-aged obese women were accompanied by significant improvements in different cardiovascular risk factors (insulin sensitivity, baseline insulin levels, TC or LDL-C), in spite of a significant decrease in serum adiponectin levels. Indeed, in the WL+RT group a decrease in circulating total adiponectin was found in 11 of 13 subjects ($P < 0.05$), whereas a parallel improvement in different cardiovascular risk factors (insulin sensitivity, LDL-C, etc.) was observed. In turn, in the WL group a similar diet in terms of caloric content and nutrient composition, and a loss of body mass and adipose tissue of similar magnitude were accompanied by no changes in serum adiponectin levels or lipid profile, although an increase in insulin sensitivity and a decrease in baseline insulin levels were observed.

Dissociation between insulin metabolism and circulating adiponectin

Two mechanisms could explain the dissociation of improvement in insulin metabolism from the circulating adiponectin observed in the WL+RT group. First, a decreased amount of circulating adiponectin, in parallel to an insulin-sensitizing effect of resistance training associated with increases in adiponectin receptor expression should not be discarded. Available evidence suggests that a relationship between aerobic exercise and adiponectin-mediated increases in insulin sensitivity is more likely to occur at the level of receptor expression in skeletal muscle (16). Second, Abbasi *et al.* (17) reported that it is possible to dissociate improvements in insulin metabolism with weight loss from circulating adiponectin, concluding that other factors (e.g., other adipokines or cytokines produced in adipose tissue or elsewhere) may play a role in the improvement of insulin sensitivity. In our study, a marked relation was observed in the WL+RT group between changes in leptin (Δ leptin) and concomitant changes in circulating insulin levels and HOMA value, these correlations being also present in the whole group ($n = 34$) before the start of the study. These results agree with a previous study by Ryan (6) that reported the effects of 16 weeks of a WL+RT program in obese postmenopausal women, concluding that the increase in insulin action may be related to

the decrease in leptin levels that were mediated by the loss of body fat. It is known that leptin regulates insulin sensitivity and glucose homeostasis via two different pathways: one through an adiposity-dependent mechanism, by controlling energy balance and body fat (increased body adiposity leads to insulin resistance), and the other through an adiposity-independent pathway mediated by the CNS (18,19). Moreover, in our study the change in total body fat ($P < 0.001$) was the most significant factor impacting on the variation in baseline insulin levels (64% of its variance), even after accounting for the effects of age and changes in energy intake, thigh muscle, leptin, fat in diet, VAT and SAT in a multiple linear regression analysis.

Effect of resistance training on TC and LDL-C

The results of the present study demonstrate a favorable response of plasma TC and LDL-C to resistance training. Indeed, after 16 weeks of intervention, while the lipid profile showed no modification in the WL group, the hypercholesterolemic women in the WL+RT group experienced a significant decrease in TC and LDL-C (Table 2). These results are in disagreement with most interventional studies, which show no improvement in lipid profiles after PRT in adult men (20) or women (12,21). Indeed, two recent reviews have concluded that resistance training does not seem to alter blood lipid and lipoprotein levels (10,22). For Braith and Stewart (10) a possible explanation for the lack of significant lipoprotein-lipid changes with PRT may be the fact that TC values for most study groups have been ≤ 200 mg/dl at study entry. Individuals with normal lipid profiles may require greater exercise stimulus and energy expenditure, coupled with significant reductions in body weight, to further improve lipid profiles. Surprisingly, no change in lipid profile was found in the WL group even though no significant differences were observed between the WL and WL+RT groups either in improvement in insulin sensitivity or in diet and habitual caloric expenditure, or in body/fat mass loss. Whereas no clear dose-response relation between weight loss and lipid modulations could be determined, it would appear that trials that experience a weight reduction $>5\%$ of initial body weight seem to observe the most significant changes in TC and LDL-C concentrations (23). However, this was not the case with our WL group, in which a decrease of $\sim 6\%$ was not translated into an improvement in lipid profile. In view of these findings, it may be assumed that chronic resistance exercise was the main factor responsible for the lipid profile improvement in our WL+RT group. This suggestion is in agreement with the results of Fahlman *et al.* (24), who reported that 10 weeks of resistance training at a rate of three sessions/week in overweight older women significantly improved the lipid profile without concurrent changes in weight or diet.

Effect of resistance training on HDL-C

As to the significant decrease of HDL-C in the WL+RT group, this finding agrees with most of the results in the literature. Indeed, a review by Durstine *et al.* (22) concluded that in women, when bodyweight loss is induced by either dietary intervention, alone or in combination with exercise, a majority

of studies indicate that HDL-C will decrease or not change. At present, we are unable to find any plausible explanation for this decrease in serum HDL-C. In our study no correlation was found between the variation of this lipid variable and any other physiological or metabolic factors. Different authors have reported that in nondiabetic individuals, and also in type 2 diabetic patients, circulating adiponectin is positively associated with plasma HDL-C and negatively correlated with LDL-C and triglycerides (25). In this context, a recent study reported that hypo adiponectinemia was independently associated with increased postheparin plasma hepatic lipase activity, which in turn could result in reductions in HDL-C (26). Of note in our study was that the difference between baseline and final concentration of adiponectin (Δ adiponectin) in the WL group significantly correlated to the concomitant changes in Δ HDL-C ($r = 0.699$, $P < 0.05$). However, no relation was found between serum adiponectin and any lipid profile variable, either in the whole group ($n = 34$) before the start of the study or after 16 weeks of intervention in the WL+RT group. Interestingly, the most significant factor impacting on TC in this WL+RT group (95% of its variance) was LDL-C, even after accounting for the effects of age, BMI, fat in diet, thigh muscle, VAT, SAT, and adiponectin in a multiple linear regression analysis.

Increased serum adiponectin levels may not always be beneficial in terms of good health

One could speculate about the physiological meaning of a significant decrease in serum adiponectin in hypercholesterolemic obese women submitted to a PRT program plus a weight-loss diet. Although a state of opinion has been created assuming that increased adiponectin levels are beneficial in terms of good health and low circulating concentrations of this hormone have been shown associated to metabolic and cardiovascular disease (3,8,9), in recent years different authors have emphasized that increased adiponectin levels may not always be beneficial (27,28). Hadjadj *et al.* (27) reported increased levels of adiponectin associated with diabetes-related microvascular complications. More recently, Dekker *et al.* (28) found that, after adjustment for cardiovascular risk factors, high adiponectin was significantly associated with increased all-cause and cardiovascular mortality.

The present study has several limitations. First, the lack of multiisoforms and receptors of adiponectin. In fact, the results found in this study may be explained by a change in these multiisoforms and/or the expression of adiponectin receptors. However, although the mechanism responsible for the decreased circulating adiponectin cannot be discerned, to the best of our knowledge this is the first time in which such a physiological adaptation (i.e., decrease in serum adiponectin with a parallel improvement in insulin sensitivity and other cardiovascular risk factors) has been observed as a result of an ordinary nonpharmacological treatment of obesity. Second, the different ovarian functional status in women. However, this limitation was avoided measuring basal circulating estradiol levels (Table 2) and balancing menopausal and perimenopausal women between groups.

In conclusion, our results agree with some previous studies indicating that there are major controversies around the real physiological meaning of increases in circulating adiponectin that need to be solved. Moreover, future studies are needed to determine whether the mechanism of the decreased circulating adiponectin found in the present study can be explained by a change in the multiisoforms and/or the levels of receptor expression of this hormone.

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DISCLOSURE

The authors declared no conflict of interest.

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