

# Treatment of Obese Adolescents: The Influence of Periodization Models and ACE Genotype

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The aims of the present study were to compare the effects of two periodization models on metabolic syndrome risk factors in obese adolescents and verify whether the angiotensin-converting enzyme (ACE) genotype is important in establishing these effects. A total of 32 postpuberty obese adolescents were submitted to aerobic training (AT) and resistance training (RT) for 14 weeks. The subjects were divided into linear periodization (LP,  $n = 16$ ) or daily undulating periodization (DUP,  $n = 16$ ). Body composition, visceral and subcutaneous fat, glycemia, insulinemia, homeostasis model assessment of insulin resistance (HOMA-IR), lipid profiles, blood pressure, maximal oxygen consumption ( $VO_{2max}$ ), resting metabolic rate (RMR), muscular endurance were analyzed at baseline and after intervention. Both groups demonstrated a significant reduction in body mass, BMI, body fat, visceral and subcutaneous fat, total and low-density lipoprotein cholesterol, blood pressure and an increase in fat-free mass,  $VO_{2max}$ , and muscular endurance. However, only DUP promoted a reduction in insulin concentrations and HOMA-IR. It is important to emphasize that there was no statics difference between LP and DUP groups; however, it appears that there may be bigger changes in the DUP than LP group in some of the metabolic syndrome risk factors in obese adolescents with regard to the effect size (ES). Both periodization models presented a large effect on muscular endurance. Despite the limitation of sample size, our results suggested that the ACE genotype may influence the functional and metabolic characteristics of obese adolescents and may be considered in the future strategies for massive obesity control.

*Obesity* (2010) **18**, 766–772. doi:10.1038/oby.2009.247

## INTRODUCTION

The prevalence of overweight and obesity is increasing at an alarming rate in children and adolescents worldwide (1). This is of great concern, given that many adverse effects on health associated with adult obesity are already being seen in obese adolescents, including metabolic syndrome risk factors (visceral obesity, hypertension, type 2 diabetes, dyslipidemia, nonalcoholic fatty liver diseases), asthma, sleep apnea, psychological disturbances, psychosocial difficulties, and lower health-related quality-of-life scores (2).

Tsiros *et al.* (1) emphasizes that dietary interventions are more effective in achieving weight loss when combined with other strategies, such as increasing physical-activity levels and/or psychological interventions to promote behavior change. Public health guidelines primarily focus on the promotion of physical activity and steady-state aerobic training (AT), which enhances cardiorespiratory fitness and has some impact on body composition (3).

Although the majority of weight-loss programs use AT, many of the effects of resistance training (RT) on obesity and metabolic syndrome have not yet been fully understood or explained. Nevertheless, as recommended by national health organizations, a comprehensive fitness program should include AT, RT, and flexibility exercise. The reason for including RT in a comprehensive fitness program is that this type of training may promote weight loss and positively affect some metabolic parameters associated with diabetes, dyslipidemia, heart disease, and cancer control. Therefore, RT reduces several risk factors associated with many diseases and physical ailments, in addition, improving quality of life and preserving functional capacity (1,3,4).

It is believed that intensity and volume are the main factors producing the effects of RT on the body. These characteristics of RT can be varied in a planned way (periodization) in order to maximize the principle of overload, and thus ensure the correct stress/recovery relationship (5). Linear periodization

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Received 30 October 2008; accepted 22 June 2009; published online 13 August 2009. doi:10.1038/oby.2009.247

(LP) and daily undulating periodization (DUP) are two known forms of periodization used to elicit maximum strength (6) in relation to nonperiodized-RT programs. Because weight loss is dependent on a negative calorie balance, for a better understanding of the effects of LP and DUP on these variables, it is important to equalize volume and intensity of both models (6,7). Notwithstanding, the effects of both periodization models on metabolic syndrome control in obese adolescents are unclear.

Muscular strength and skeletal muscle mass are important for the performance of day-to-day activities and to avoid diseases such as type 2 diabetes (8) and the effects of training on both muscular phenotypes have a genetic component (9). Angiotensin-converting enzyme (ACE) has been suggested as being able to influence baseline muscle strength (9) and skeletal muscle mass (10) as well as changing these phenotypes in RT (11).

Thus, the first aim of the present study was to compare the efficiency of LP and DUP with regard to metabolic syndrome risk factors, resting metabolic rate (RMR), and muscular endurance in obese adolescents of both genders. A pilot exploratory analysis about the influence of the ACE genotype was performed within these same parameters.

## METHODS AND PROCEDURES

### Subjects

A total of 32 postpuberty obese adolescents (BMI > 95th percentile of the CDC reference growth charts) (12), aged  $16.50 \pm 1.74$  years, including 15 boys and 17 girls were recruited. The inclusion criteria for the postpubertal stage were based on Tanner (stage five) for boys (13) and girls (14). The exclusion criteria were: (i) an identified genetic disease, (ii) metabolic or endocrine diseases, (iii) chronic alcohol consumption, (iv) previous use of drugs such as glucocorticoids, anabolic-androgenic steroids, insulin sensitizers, or psychotropics, which may affect appetite regulation, and (v) pregnancy. The study was conducted in accordance with the principles of the Helsinki Declaration and was formally approved by the ethics committee of the Federal University of São Paulo–Paulista Medicine School (Number: 0135/04).

Subjects were randomly divided into two groups: (i) a group that performed 12 weeks of LP RT ( $n = 16$ , eight girls and eight boys) and (ii) a group that performed 12 weeks of DUP RT ( $n = 16$ , nine girls and seven boys). Before the periodization, both groups performed 2 weeks of similar training for adaptation, totaling 14 weeks of protocol. All subjects reported not having had experience of RT before the study. The evaluations were made at two different times, baseline and after 14 weeks of multidisciplinary therapy. All subjects were completely familiarized with all testing procedures before the experiment to reduce the influence of any learning effects, solely due to the mechanics of performing the test protocol.

### Anthropometric measurements and body composition

Subjects wearing light clothing and no shoes were weighed on a Filizola scale (Filizola, São Paulo, Brazil) to the nearest 0.1 kg. Stature was measured to the nearest 0.5 cm by using a wall-mounted stadiometer (model Es 2030; Sanny, São Paulo, Brazil). BMI was calculated as body weight divided by height squared ( $\text{wt}/\text{ht}^2$ ). Body composition was measured by Plethysmography in the BOD POD body composition system (version 1.69; Life Measurement Instruments, Concord, CA) (15).

### Visceral and subcutaneous adiposity measurements

All abdominal ultrasonography procedures and measurements of visceral and subcutaneous fat were performed double-blinded by the same physician specialized in diagnostic imaging using a 3.5-MHz

multifrequency transducer (broad band). This procedure allows a reduction in the risk margin for misclassification. The intra-examination coefficient of variation for the ultrasonography was 0.8%. Ultrasonography measurements were taken for intra-abdominal (“visceral”) and subcutaneous fat. Ultrasonography-determined subcutaneous fat was defined as the distance between the skin and external face of the rectus abdominis muscle, and visceral fat was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta as previously described by Ribeiro-Filho *et al.* (16), Tock *et al.* (17), De Piano *et al.* (18), and Dâmaso *et al.* (19).

### Serum analysis

Blood samples were collected in the outpatient clinic around 0800 h after an overnight fast. After collection, the blood was centrifuged for 10 min at 5,000 r.p.m. and stored at  $-20^\circ\text{C}$  for future analyses. The materials used for collection were disposable, adequately labeled and of recognized quality. Blood was collected by a skilled and qualified technician. Insulin resistance was assessed by homeostasis model assessment of insulin resistance index (HOMA-IR). HOMA-IR was calculated by the product of blood glucose (fasting blood glucose) and the immunoreactive insulin (I): (fasting blood glucose (mg/dl)  $\times$  I (mU/l))/405. All variables were analyzed using a commercial kit (CELM, Barueri, Brazil).

### Maximal oxygen consumption tests

Maximal oxygen consumption ( $\text{VO}_{2\text{max}}$ ) was determined using a graded exercise test on a Life Fitness (Model TR 9700HR; Falmouth, KY) motor-driven treadmill by using a modified Bruce protocol (20). During each stage of the test, heart rate was monitored continuously with a cardiometer (Polar–Model FS1 dark blue; Lake Success, NY). Continuous respiratory gas analysis and volume measurements, oxygen uptake ( $\text{VO}_2$ ), and carbon dioxide production ( $\text{VCO}_2$ ) were performed breath by breath with a ventilated-hood system (Model Quark PFT Ergo; COSMED, Rome, Italy). Prior to each test, internal gas and volume calibrations were performed with certified gases of known standard concentrations, and the temperature was controlled at  $21\text{--}24^\circ\text{C}$ .

### RMR

The RMR was measured by indirect calorimetry with a ventilated-hood system (Model Quark PFT Ergo; COSMED). RMR was measured as previously described by Haugen *et al.* (21). Subjects rested quietly in a supine position in an isolated room with the temperature controlled at  $21\text{--}24^\circ\text{C}$ . The subjects remained at rest for 15 min before the measurements were performed. Oxygen consumption as well as carbon dioxide production in the expired air was measured as suggested by Compher *et al.* (22). RMR was estimated according to equations proposed by Weir (23).

### Muscular endurance assessments

After anthropometric evaluations, muscular endurance tests were performed 15 repetitions maximal (15RM). All subjects were familiarized with the test 48 h after the tests with the equipment used. The exercises selected were bench press and leg press; each test was separated by 48 h; in the previous and test weeks, participants avoided any other type of exercise. After a general warm-up (10 min of low-intensity treadmill running), individuals performed of 15RMs with progressively heavier weights until maximal 15 repetitions were determined within three attempts, using 3- to 5-min rest periods between trials. The standardization of range of motion and movement of the exercises was conducted according to the descriptions of Brown and Weir (24).

### ACE genotyping

Blood samples were obtained from all subjects in vacutainer tubes (BD Biosciences, Franklin Lakes, NJ). Genomic DNA was extracted from peripheral blood leucocytes using ChargeSwitch dDNA Blood Kits (Invitrogen, São Paulo, Brazil). ACE ID genotype was determined by PCR using a published 3-primer method that included an I-specific oligonucleotide that produce unambiguous results for the ACE genotype. Briefly, the sequences of the sense and antisense primers used to amplify

the region of *Alu* insertion, with the *Alu* element's presence or absence of *Alu* element were (F: 5'-CTGGAGACCACTCCCATCCTTCT-3' and R: 5'-GATGTGGCCATCACATTCGTCAGAT-3'). PCR amplification was performed in a final volume of 25  $\mu$ l that containing 10  $\mu$ l of DNA, 5  $\mu$ l of DNA buffer, 2.5  $\mu$ l of MgCl<sub>2</sub>, 1.0  $\mu$ l of deoxynucleotide triphosphate, 0.5  $\mu$ l of each primer, 0.5  $\mu$ l Taq DNA polymerase, and 5  $\mu$ l of H<sub>2</sub>O milli-Q. The cycling conditions were 95°C for 5 min, and then cycled 35 times through the following steps: 95°C for 45 s, 60°C for 45 s, 72°C for 45 s, and 72°C for 7 min. Amplicons were resolved in 2% agarose gel with ethidium bromide staining, being visualized as a 490-base pair band, corresponding to the I allele, and 190-base pair band, corresponding to the D allele. Whenever a D/D type was identified according to the results of the described PCR, a second, independent PCR amplification was performed with I-specific sequence primers (F: 5'-CTGGAGACCACTCCCATCCTTCT-3' and 5'-GTCTCGATCTCCTGACCTCGTG-3'). In this second reaction, PCR conditions were unchanged.

### Intervention procedures

The multidisciplinary obesity intervention consisted of AT + RT, clinical, nutritional, and psychological therapy. The use of multidisciplinary therapy as a criterion has been suggested by World Health Organization (25) and Dâmaso *et al.* (19). All measurements were performed at baseline and after the 14-week therapy.

### Exercise protocols

All the individuals performed three training sessions per week, consisting of a therapy of combined exercises (AT + RT). At each training session, subjects were instructed to invert the order of the exercises; that is, in one session, the individual started the training session with AT, and in the subsequent session, the same individual started with RT.

**AT.** The duration of AT was 30 min/session. The exercise mode was running performed on a motor-driven treadmill (Life Fitness-Model TR 9700HR). The exercises were done at the cardiac frequency intensity of the ventilatory threshold I ( $\pm$ 4 bpm). The physiologists controlled the cardiac frequency, which was measured with a cardiometer at intervals of 5 min during all training sessions (Polar-Model FS1 dark blue).

**RT.** The duration of RT was about 30 min/session. Training was divided following the recommendations of American College of Sports Medicine (26). The exercise and order of exercise was strictly followed by both groups, as presented in Table 1. All sessions were supervised individually by an experienced RT professional.

Volume and intensity were modified differently for each group (Table 2). However, volume (total repetitions performed) and intensity were equal for LP and DUP groups. In this context, the difference between groups was the time and sequence of load application.

**Adaptation to training.** The first 2 weeks were for adaptation to training, learning the movement and were similar for both groups (three sets of 15–20RM) (Table 2); all subjects performed the same exercises previously mentioned (Table 1).

LP group followed the load application as presented in Table 2; each microcycle lasted 4 weeks. In the first microcycle (weeks 3–6), the participants performed three sets of 15–20RM, in the second microcycle (weeks 7–10) three sets of 10–12RM, and in the third microcycle (weeks 11–14) three sets of 6–8RM (Table 2).

DUP in day 1 (Mondays) participants trained three sets of 15–20RM and day 2 (Wednesdays) three sets of 10–12RM, and day 3 (Fridays) three sets of 6–8RM (Table 2). This scheme was repeated during the 12 weeks after the adaptation phase.

The rest interval between series and exercises were: 15–20RM = 45 s; 10–12RM = 1 min, and 6–8RM = 1.5 min. The periodization models applied were based on our previous studies (27) and others published in the literature (7,28). The training loads were adjusted in each training

session and evaluated according to increase in participants' strength; that is, the training was conducted with maximal repetitions.

### Nutritional therapy

The adolescents received nutritional therapy once a week (for 1 h) during 14 weeks of therapy. Nutritional education is concerned with changing nutritional behavior as well as providing information about qualitative and quantitative aspects of food requirements. The aim of this therapy was to provide changes in poor energy-intake habits during the weight-loss phase.

Energy intake was set at the levels recommended by the dietary reference intake for subjects of the same age and gender with low levels of physical activity (29). The subjects were encouraged to reduce their food intake and to follow a balanced diet according to reference values obtained after baseline RMR measurement. A target of 5–10% of baseline weight was used as an initial weight-loss goal. Baseline and postintervention food intake were assessed by a 3-day record, previously described by Piano *et al.* (18). All dietary consumption data were analyzed by Nutwin software, version 1.5 (UNIFESP, 2003, São Paulo, Brazil).

### Psychological therapy

Psychological therapy was established by validated questionnaires, taking into account some of the psychological problems caused by obesity, as described in the literature including depression, eating disorders, anxiety, decreased self-esteem, and body-image disorders (30). During the multidisciplinary therapy, the adolescents received psychological orientation for 1 h in a weekly group session. The psychologist discussed body image and eating disorders, such as bulimia and anorexia nervosa, and binge eating disorders as well as their signs, symptoms, and consequences for health; the relationship between feelings and food; familiar problems such as alcoholism and other issues. Individualized psychological therapy was recommended when weight problems or poor-dietary habits were found.

### Clinical therapy

To accomplish their health and clinical parameters, the patients visited the endocrinologist once per month.

**Table 1 Resistance training protocol**

Exercises and order of exercises (RT)	
1. Bench press	6. Lower back
2. Leg press	7. Military press
3. Sit-ups	8. Calf raises
4. Lat pull-down	9. Arm curls
5. Hamstring curls	10. Triceps pushdown

The protocol was performed during 14 weeks of LP and DUP, three weekly sessions (Monday, Wednesday, and Friday). RT, resistance training.

**Table 2 Resistance training program for both groups**

LP group <sup>a</sup>			
Weeks 1–2 <sup>c</sup>	Weeks 3–6	Weeks 7–10	Weeks 11–14
Three sets 15–20RM	Three sets 15–20RM	Three sets 10–12RM	Three sets 6–8RM
DUP group <sup>b</sup>			
Weeks 1–2 <sup>c</sup>	Day 1	Day 2	Day 3
Three sets 15–20RM	Three sets 15–20RM	Three sets 10–12RM	Three sets 6–8RM

DUP, daily undulating periodization; LP, linear periodization; RM, repetitions maximal.

<sup>a</sup>14 Weeks of LP. <sup>b</sup>14 Weeks of DUP. <sup>c</sup>Weeks for adaptation.

**Table 3 Anthropometrics, biochemical, and physiological variables for LP and DUP groups**

Variable	LP (n = 16)			DUP (n = 16)			LP vs. DUP	
	Baseline	After intervention	ES	Baseline	After intervention	ES	Baseline P	After intervention P
Height (cm)	165 ± 8	165.3 ± 7.9	0.03	169.1 ± 8.0	169.3 ± 8.3	0.02	0.17	0.15
Body mass (kg)	98.9 ± 13.5	90.3 ± 12.7**	0.63	107.6 ± 12.2	96.9 ± 11.4**	0.87	0.81	0.15
BMI (kg/m <sup>2</sup> )	36.5 ± 5.6	33.2 ± 5.2**	0.58	37.7 ± 4.4	33.8 ± 4.4**	0.88	0.51	0.73
Body fat (%)	45.5 ± 8	38.3 ± 9.5**	0.90	45.1 ± 8.3	31.7 ± 10.1**	1.6	0.89	0.78
Body fat (kg)	43.7 ± 11	34 ± 11.7**	0.88	48.8 ± 11.4	36.6 ± 12.4**	1.07	0.25	0.57
Fat-free mass (kg)	53.3 ± 6	55.1 ± 7.7*	0.3	58.8 ± 9.9	60.2 ± 9.6*	0.14	0.09	0.12
Visceral fat (cm)	4.3 ± 0.2	2.8 ± 0.8**	0.75	4.4 ± 1.5	3.2 ± 1**	0.8	0.75	0.28
Subcutaneous fat (cm)	3.6 ± 0.4	3.1 ± 0.6*	1.25	3.6 ± 0.6	3 ± 0.6**	1.0	0.88	0.68
Glucose (mg/dl)	89.6 ± 6.6	88.8 ± 5.3	0.12	89.3 ± 6.8	89.5 ± 5.2	0.02	0.90	0.74
Insulin (μU/dl)	15.4 ± 3.4	13.6 ± 5.2	0.52	19.7 ± 4.7	14 ± 3.9**	1.21	0.66	0.86
HOMA-IR	3.4 ± 1.31	3.1 ± 1.9	0.22	4.3 ± 1.3	3.1 ± 1.2**	0.92	0.18	0.78
Total cholesterol (mg/dl)	163 ± 30.9	146 ± 30**	0.55	178.6 ± 30.5	155.2 ± 18.2**	0.76	0.18	0.36
HDL cholesterol (mg/dl)	42.2 ± 6	42.7 ± 5.1	0.21	42.1 ± 7.7	43.8 ± 9	0.24	0.97	0.69
LDL cholesterol (mg/dl)	104 ± 26.9	89.8 ± 27.5**	0.52	117.1 ± 27.2	94.2 ± 16**	0.84	0.22	0.61
SBP (mm Hg)	130.4 ± 14.5	111.8 ± 6.7**	1.28	136.7 ± 17.2	118.3 ± 9.0**	1.06	0.42	0.08
DBP (mm Hg)	81.4 ± 10.8	71.8 ± 5.4**	0.92	85.3 ± 5.1	74.0 ± 5.1**	2.21	0.22	0.26
VO <sub>2max</sub> (ml/kg/min)	27.5 ± 6.8	30.3 ± 8.1**	0.41	24.7 ± 5	28 ± 6.6**	0.66	0.21	0.43
RMR (kcal)	1,847.2 ± 407.9	1,591.7 ± 361.8*	0.62	1,873.3 ± 575	1,819.7 ± 506.4	0.09	0.81	0.08

Values were expressed by mean ± s.d.

DBD, diastolic blood pressure; DUP, daily undulating periodization; ES, effect size; HOMA-IR, homeostasis model assessment-insulin resistance; LP, linear periodization; RMR, resting metabolic rate; SBP, systolic blood pressure; VO<sub>2max</sub>, maximal oxygen consumption.

\*Differences between baseline vs. after intervention ( $P < 0.05$  measured by paired  $t$ -test). \*\*Baseline vs. after intervention ( $P < 0.01$  measured by paired  $t$ -test).

### Statistical analysis

All statistical analyses were conducted using Statistica 6.1 (StatSoft, Tulsa, OK). The data were presented as mean ± s.d. Data were tested for normal distribution using the Shapiro–Wilk  $W$ -test. To determine whether there were any differences between the groups (DUP vs. LP) in the baseline or after intervention, the unpaired Student's  $t$ -test was used. To determine whether there were any differences between the periods (baseline vs. after intervention) for each sample periodization group, the paired Student's  $t$ -test was used. The repeated-measures ANOVA (two way) was used to analyze differences between ACE genotype group (II, ID, and DD), baseline vs. after intervention and interaction between genotype group and time. When the difference presented was significant, the Tukey's unequal post hoc test for multiple comparisons was applied. A critical level of  $P \leq 0.05$  was established. The effect size (ES) was used for determining only the magnitude of treatment effect (Pre–Post ES = (Post-test mean – Pretest mean)/Pretest s.d.). The magnitude of effect on untrained individuals is trivial:  $<0.50$ ; small:  $0.50$ – $1.25$ ; moderate:  $1.25$ – $1.90$ ; large:  $>2.0$  (31).

### RESULTS

The results presented in this study were divided into two analyses: first the groups were assigned by periodization models (LP and DUP); and in the second analysis the obese adolescents were separated according to the genes of the ACE (II, ID, and DD).

### Effects of linear and DUP

**Tables 3** and **4** presents the effects between the two models of periodization analyzed in the present investigation into anthropometric, biochemical and physiological characteristics, and muscular endurance of obese adolescents. Indeed, the comparison was made between the values at baseline and after intervention for each sample group.

Statistical analysis with Student's  $t$ -test showed no significant differences between LP and DUP groups ( $P > 0.05$ ), for all parameters at baseline and after intervention (**Tables 3** and **4**).

Significant reductions were observed in both groups after intervention, in body mass, BMI, percent-body fat, body fat (kg), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, low-density lipoprotein cholesterol, visceral ( $P < 0.01$ ) and subcutaneous fat ( $P < 0.05$ ). On the other hand, a significant increase in fat-free mass, VO<sub>2max</sub> and muscular endurance was observed. However, only the DUP was effective in promoting a reduction in the insulinemia and HOMA-IR ( $P < 0.01$ ), but they did not differ between LP and DUP in all parameters. RMR was reduced in the LP group ( $P < 0.05$ ) and was maintained in the DUP group (**Tables 3** and **4**).

When the ES of periodization models was analyzed, the magnitude of effect was higher in the DUP than the LP group

**Table 4 Muscular endurance alterations during 14 weeks of training for LP and DUP groups**

Group	LP	DUP	LP vs. DUP
	X ± s.d.	X ± s.d.	P
Bench press (kg)			
Baseline	14.6 ± 6.7	14.51 ± 7.3	0.98
After intervention	34 ± 10.6**	39.56 ± 12.9**	0.22
% Change	175.8 ± 118.6**	219.504 ± 133.4**	0.09
ES	2.78	3.43	—
Leg press (kg)			
Baseline	48.6 ± 21.8	45 ± 20.1	0.70
After intervention	200.2 ± 22.9**	210.8 ± 39.2**	0.45
% Change	395.5 ± 219.8**	455.3 ± 248.4**	0.32
ES	6.96	8.25	—

Values were expressed by mean ± s.d.

DUP, daily undulating periodization; ES, effect size; LP, linear periodization.

\*\*Difference between baseline vs. after intervention ( $P < 0.01$  measured by paired  $t$ -test).

in body fat (%) (LP: small and DUP: moderate), HOMA-IR and  $VO_{2max}$  (LP: trivial and DUP: small), DBP (LP: small and DUP: large); whereas, the ES was higher in the LP than the DUP group in subcutaneous fat (LP: moderate and DUP: small) and SBP (LP: moderate and DUP: small). In muscular endurance, both groups presented a large ES in the bench press and leg press (Tables 3 and 4).

#### Influence of the ACE insertion/deletion genotype

Supplementary Tables S1 and S2 online presents the anthropometric, biochemical, and physiological profile of the groups separated by genotypes (II, ID, and DD), and the comparison between the groups, time, and interaction between genotype and time (measured by ANOVA). It is important to note that there was no interaction between genotype and time.

Body mass, BMI, fat-free mass, and visceral fat did not differ between the groups. The percentage of body fat at baseline was higher in the ID than II genotype ( $P = 0.042$ ). It was observed that II showed higher values of  $VO_{2max}$  when compared with ID and DD, as well as in RMR compared to DD (see Supplementary Table S1 online).

When we compared the baseline and after intervention times, a reduction in the three genotype groups was observed in body mass, BMI, percentage of body fat and absolute body fat, low-density lipoprotein cholesterol ( $P < 0.01$ ). Fat-free mass and high-density lipoprotein cholesterol were increased and RMR was decreased only in group II ( $P < 0.01$ ). Visceral fat, subcutaneous fat, cholesterol total, and blood pressure were decreased in ID. Indeed, a significant reduction was observed in visceral fat, DBP, and an increase in the  $VO_{2max}$  of DD genotype ( $P < 0.01$ ) (see Supplementary Table S1 online). Finally, a expressive increase and large ES ( $ES > 2.00$ ) on muscular endurance was observed in the bench press and leg press (see Supplementary Table S2 online).

#### DISCUSSION

Many studies have examined the effects associated with diet-induced and diet + exercise-induced weight loss, including assessment of body composition, exercise performance, RMR, serum lipid profile, and strength. However, few investigations have looked at all these effects simultaneously, and no studies were found in response to different RT-periodization models such as LP and DUP. Thus, the present study investigated the effects of the two periodization models LP and DUP, associated with multidisciplinary intervention.

It is well established that AT is an important method for successful weight loss, particularly when associated with a hypocaloric diet (1). However, some years ago, it was reported that low intensity, longer duration aerobic exercise combined with high-repetition RT was the most effective for weight management (32).

Considering that volume and intensity can exert an influence on energy expenditure, would the periodization model be more efficient in the control of obesity and metabolic syndrome risk factors when these variables are equalized?

In this study, after intervention the LP and DUP groups experienced similar reductions in body mass, BMI, absolute and relative body fat, and increase in fat-free mass (Table 3). Our findings are in agreement with those observed by Kraemer *et al.* and Lazzer *et al.* (28,33). These results could be associated with the expenditure of energy and great activation of the metabolism during and after exercise, since the groups performed aerobic exercise + RT (Table 3).

In previous studies, it was proposed that the II genotype could allow a more positive energy balance to be conserved during training, resulting in an enhanced metabolic efficiency (34,35). Such metabolic efficiency could have allowed our II homozygotes to have energy available to increase fat-free mass despite the caloric restriction imposed in the present study, when comparing baseline with after intervention values (see Supplementary Table S1 online).

In the present study, the LP group showed a significant reduction in RMR ( $P < 0.05$ ) after weight loss, whereas the DUP group maintained it (Table 3). One possible explanation is that DUP altered the magnitude of the stimuli in each session; this phenomenon could have had a greater influence on homeostasis, increasing the energy expenditure, hormone levels, and excess postexercise oxygen consumption (although, these data were not evaluated in the present study). As this study is the first to show such results, further investigations are necessary for better understanding of these different adaptations.

With regard to visceral fat and subcutaneous fat, Parr and Haight (36) mentioned that the site of fat distribution is more important than total body fat because abdominal obesity is associated with an increased risk for several comorbidities. Sharma (37), however, indicated that the mechanisms that link this adipose tissue deposit to components of the metabolic syndrome, such as hypertension are not clear (38). Adipose tissue expresses components of the renin-angiotensin system (39) and also has angiotensin II receptors (40).

In the present study, the effects of a multidisciplinary intervention on visceral adipose tissue were different in relation to ACE polymorphism (see **Supplementary Table S1** online). Another research demonstrated that obese women, who previously presented high levels of ACE in adipose tissue, presented high blood pressure as well as ACE; which were reduced after 13 weeks of a hypocaloric diet (39).

Insulin resistance, or a reduction in the rate of glucose disposal elicited by a given insulin concentration, is present in individuals who are obese (4). HOMA-IR is an insulin-resistance index. AT and RT have been shown to be important nonpharmacological tools in the control of insulin resistance. Both exercises have been shown to improve the rate of glucose use, increase the glycogen storage rate, and potentiate the intracellular mechanisms that increase the expression of glucose transporter 4 in the skeletal muscle and adipose tissue, increase the sensitivity to insulin and normalize glucose tolerance (41), and it could be that the exercise intensity may influence this mechanism.

It is important to note that only the DUP group presented a significant reduction in insulin concentration and HOMA-IR ( $P < 0.01$ ) (**Table 3**). This could have occurred due to the greater intensity of the exercise experimented in the DUP group right from the beginning of the intervention, the time when the body of the individual resistant to insulin is more susceptible to the effects of a diet and exercise. Another hypothesis for this finding could be that the DUP group had a tendency to present a higher value at baseline than the LP group, although it was not statistically significant ( $P = 0.66$ ).

All together, these results of DUP may, in the near future, represent a gateway to improving metabolic syndrome risk factors in this special population.

In blood pressure, both LP and DUP diminished SBP and DBP (baseline vs. after intervention,  $P < 0.01$ ), in spite of the mean values being within the values of normality, these alterations showed an efficient effect of combined exercise on these metabolic syndrome components. However, it is intriguing to note that the LP appears to indicate that there may be a bigger magnitude of change in SBP (ES = LP: 1.28 and DUP: 1.06), whereas in DUP, it appears that there may be a bigger change in the DBP control (ES = LP: 0.92 and DUP: 2.21) (**Table 3**). Not only the increase in body weight, but particularly the increase in visceral fat is correlated with the increase in blood pressure. The reduction in SBP and DBP found in the present study can be explained by the reduction in visceral fat (**Table 3**). Thus, Simon *et al.* (42) pooling results from a number of interventional studies, estimated that a weight loss of 9.2 kg is associated with a reduction of 6.3 mm Hg SBP and 3.1 mm Hg DBP. Another fact that explains these results is the systematic performance of exercise. Interestingly, in the present investigation only D allele carriers demonstrated a reduction in diastolic (ID, DD) or SBP in comparison with II homozygotes (see **Supplementary Table S1** online). As mentioned before, this could be related to the reduction observed as regards visceral adipose tissue.

The increase in  $VO_{2max}$  was found in both groups ( $P < 0.01$ ), and it is important to note that DUP resulted in a higher ES

than that observed in the LP (ES = DUP: 0.56 and LP: 0.41) (**Table 3**).

One of the proposals of this study was to compare muscular endurance gains of two different periodized programs. This is the first study to compare LP and DUP programs for muscular endurance in obese adolescents. The results demonstrated that both groups significantly increased muscular endurance performance ( $P < 0.01$ ) and presented a large ES (ES > 2.0) irrespective of the ACE genotype (**Tables 4** and **Supplementary Table S2** online).

This increase in muscular endurance is important for the obese individual, particularly for performing day-to-day activities. Rhea *et al.* (7) mentioned that the increased muscle function, improved performance efficiency and the reduction in body mass may increase relative maximal oxygen uptake. In the same study, the authors compared LP, DUP, and reverse LP and verified that the three periodization models increased muscular endurance, and there was no difference between LP and DUP in muscular endurance, similar to our findings.

In conclusion, it is important to emphasize that there was no static difference between LP and DUP groups in all analyzed parameters, showing that multidisciplinary intervention was the determining factor for improvement of health parameters examined in obese adolescents undergoing 12 weeks of study. However, it appears that there may be a bigger changes in the DUP than LP group in some of the metabolic syndrome risk factors in obese adolescents with regard to the ES. Our next step is to check whether there is a difference between the models of periodization (DUP vs. LP) after long-term multidisciplinary therapy.

Despite the simple size limitation, our results suggested that the ACE genotype may have an influence on the functional and metabolic characteristics of obese adolescents, however, it is necessary for this to be confirmed in future studies.

#### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.us.nature.com/oby>

#### ACKNOWLEDGMENTS

AFIP, CNPq, CAPES, FAPESP 2006/00684-3 and 2008/53069-0, FAPESP (CEPID/Sleep #9814303-3 S.T.), CENESP, FADA, and UNIFESP, supported the CEPE/GEO-Multidisciplinary Obesity Intervention Program.

#### DISCLOSURE

The authors declared no conflict of interest.

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