



Effects of anabolic steroid treatment associated with physical training in adipose tissue of male Wistar rats

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ABSTRACT. Anabolic androgenic-steroids (AAS) include a broad class of synthetic derivatives of testosterone, being nandrolone decanoate the most widely used in sports environment. The aim of this study was to evaluate the metabolic effects of nandrolone decanoate in sedentary and trained adult male rats. We established four experimental groups: sedentary control, sedentary treated, trained control and trained treated. The training had consisted of running on a treadmill for nine weeks. Treated animals received intramuscular injections of nandrolone decanoate (0.5 mg kg^{-1}) during the last four weeks of physical training. The training time as the drug used were not sufficient to significantly reduce body weight gain, but caused a significative decrease on diameter of adipocytes and in the amount of adipose tissue stored, as well as decreased the plasma levels of glucose and total cholesterol.

Keywords: adipocytes, anabolic agents, body weight, exercise, nandrolone.

Efeito do tratamento com anabolizante associado com atividade física no tecido adiposo de ratos machos Wistar

RESUMO. Os esteróides anabólicos androgênicos incluem uma ampla classe de derivados sintéticos da testosterona, sendo o decanoato de nandrolona um dos mais utilizados no meio esportivo. Este trabalho teve como objetivo avaliar os efeitos metabólicos desse anabolizante esteróide em ratos machos adultos sedentários e treinados. Foram estabelecidos quatro grupos experimentais: sedentário controle, sedentário tratado, treinado controle e treinado tratado. O treinamento consistiu de corrida em esteira ergométrica durante nove semanas. Os animais tratados receberam injeção intramuscular de decanoato de nandrolona (0.5 mg kg^{-1}) durante as quatro últimas semanas de treinamento físico. Tanto o tempo de treinamento, quanto a dose de anabolizante utilizado não foi eficiente para reduzir significativamente o ganho de peso corporal, mas causou reduções significativas no diâmetro dos adipócitos e na quantidade de tecido adiposo armazenado, assim como diminuiu os valores plasmáticos de glicose e de colesterol total.

Palavras-chave: adipócitos, anabolizante, peso corporal, exercício, nandrolona.

Introduction

Anabolic steroids or androgenic anabolic steroids (AAS) are hormones which show both anabolic – promote an increase of skeletal muscle mass – and androgenic – masculinizing effects (HANDELSMAN, 2004; KANAYAMA et al., 2008). It is common to use the term anabolic steroid for any synthetic steroid derivative of testosterone with anabolic activity higher than androgenic activity (SILVA et al., 2002). These groups of synthetic compounds have been developed for various therapeutic applications: treatment of hypogonadism, neonatal micropenis, growth retardation, and partial androgen deficiency in elderly men or in male hormonal contraception problems. Androgen therapy has also been used to

treat osteoporosis and refractory anemia (SILVA et al., 2002; CUNHA et al., 2004; CUNHA et al., 2006; CHAWLA et al., 2009). In addition, elite athletes or gym practitioners, attracted by the anabolic effects make use of these compounds (FRIZON et al., 2005).

The nandrolone decanoate is one of the most widely used derivatives of testosterone (CUNHA et al., 2006; FERMO et al., 2008), mainly because of its strong anabolic effect (FERMO et al., 2008). This selective action occurs because when nandrolone enters cell, undergoes the action of 5α -reductase, resulting in a metabolite that has low affinity for androgen receptors (SILVA et al., 2002; CUNHA et al., 2004; 2006; FERMO et al., 2008). Since the presence of 5α -reductase is lower in muscles a

higher anabolic response is elicited when compared to other tissues (SILVA et al., 2002).

Nevertheless, a list of non-physiological changes have been associated with use of high doses of this synthetic steroid, such as cardiovascular (increased blood pressure, atherosclerosis, myocardial infarction), increased secretion of the sebaceous glands of acne with over-training and seborrhea dermatitis (BOLDING et al., 2002; FRIZON et al., 2005), gynecomastia, premature epiphyseal closure, liver tumors (CUNHA et al., 2004), problems related to male reproductive system (POPE-JÚNIOR et al., 2000; SANTOS, 2003; FOLETTO et al., 2010), behavioral syndromes (POPE-JÚNIOR et al., 2000; SILVA et al., 2002) and alterations in lipid metabolism by increasing LDL and lowering HDL (KUIPERS et al., 1991; YESALIS; BAHKRE, 2000).

Lipid disorders resulting from the use of AAS suggest that adipose tissue may be an important target of these compounds and, although the mechanisms of action are not fully understood, different patterns of body fat distribution between men (android or central obesity) and women (gynoid) confirm the importance of these steroids on adipose tissue metabolism (ARNER, 2005; LOVEJOY et al., 2008).

The amount of adipose tissue in different anatomical regions depend both on the ability of adipocytes to alter their capacity to store lipids, and also the rate of proliferation of preadipocytes and subsequent differentiation into mature adipocytes. The number and size of fat cells are regulated in a coordinated manner, and there are strong evidences that various hormones (insulin, glucagon, glucocorticoids, GH, adrenaline and sex steroids) are responsible for this regulation (ARNER, 2005; LOVEJOY et al., 2008).

This study evaluated the effects of chronic use of nandrolone decanoate (deca-durabolin®) on metabolic parameters and morphometry of adipose tissue in sedentary male Wistar rats submitted to physical training.

Material and methods

Experimental animals

Male Wistar rats were kept in an animal house facility at a temperature of $23^{\circ} \pm 2^{\circ}\text{C}$, in a light:dark cycle of $12/12$ hours (lights on at 6:30 a.m.) with free access to water and rodent chow (Nuvital®, Colombo, Paraná State, Brazil). The experimental procedures were approved by the Committee of Ethics in the Use of Experimental Animals – Ceae (Protocol n. 039/2008).

Experimental procedure

Twenty-four animals aging 45 days were allotted to four experimental groups: sedentary control (SCo), sedentary treated (STr), trained control (TCo) and trained treated (TTTr), with six animals per group. The trained animals were submitted to a training program, which consisted in running (intensity of 60–65% of the VO_2 Max) in a programmable ergometer treadmill (Imbramed, mod.KT3000) tailored to train eight rats simultaneously. Before the beginning of the training, the animals had a week of adaptation, during which the speed of the treadmill increased progressively from 0.3 to 0.6 km hr^{-1} at stages lasting two min each. After this period, the speed and the duration increased gradually until 60 min. day^{-1} at an average speed of 1.0 km hr^{-1} (NEGRÃO et al., 1992; DUFLOTH et al., 1997). The training was carried out four times a week, always at the same time (7:30 to 8:30 a.m.), during nine weeks.

The treatment with nandrolone decanoate began on the fifth week and consisted of the intramuscular injections (gastrocnemius muscle) of deca-durabolin® (0.5 mg kg^{-1} body weight) diluted in vegetal oil, five times a week, during four weeks (PERES; LUCIANO, 1995; NOORAFSHAN et al., 2005). The control groups received intramuscular injections of the vehicle (vegetal oil).

Records of body weight, naso-anal length and food intake were made at intervals of five days. At the end of the training and treatment, the animals were anesthetized with pentobarbital sodium (Hypinol® 3%, 4 $\text{mg } 100 \text{ g}^{-1}$ body weight, i.p.) and then through an abdominal-pelvic laparotomy, blood samples were collected from the inferior vena cava. Finally, liver, heart, kidneys, retroperitoneal and periepididymal fat were removed and weighed. Blood samples were properly stored and later used for the measurements of glucose (plasma) and total cholesterol, triglycerides, total protein and albumin (serum), using colorimetric methods (Gold Analisa, Minas Gerais State, Brazil).

Adipocytes were isolated following the methodology established by Rodbell (1964), with some adaptations. After being removed, periepididymal fat pad was fragmented with a scissor and placed in 4 mL digestion buffer (DMEM/HEPES 25 mm, bovine albumin fraction V – BSA in 4% collagenase II 1.25 mg mL^{-1} , pH 7.4 at 37°C), for about 20 min. (37°C) under constant agitation (150 rpm in an orbital water bath shaker). Then, the digested tissue was filtered, placed in a conical tube and washed three times with 25 mL of EHB buffer (EARLE/HEPES) 20 mm, containing 1% BSA, 1 mm sodium pyruvate, without glucose, pH 7.4 at

37°C (buffer EARLE/HEPES/BSA – EHB). The diameter of adipocytes (100 cells per animal) was measured using an image analysis system (Image-Pro Plus 4.5 – Media Cybernetics). The number of cells was estimated calculating the ratio between retroperitoneal fat mass and the mass of each adipocyte isolated from the same depot. The adipocyte mass was calculated using the adipocyte diameter to determine its volume (spherical cell) and the respective area. Considering adipocyte density (i.e., an adipocyte is mainly filled with fat/oil, which density is equal 0,901 g cm⁻³) and the area of the cell the mass of each adipocyte was determined.

Statistical analysis

The statistical analysis of results was performed by the program Prism, v. 5.0 (GraphPad, USA) using two-way analysis of variance (ANOVA), followed by Tukey's test, setting the significance level of 95% ($p < 0.05$). The correlation and significance between medium adipocyte diameter and the weight of periepididymal fat pad was determined by Pearson's correlation coefficient.

Results

Figure 1 shows the evolution of body weight of sedentary and trained rats, both control and subjected to treatment with nandrolone decanoate. Values statistically different between the experimental groups were not found, however the trained group treated with nandrolone (TTr) had a final body weights 12% lower than the sedentary control group (SCo) (Table 1). Lee's index, food intake and food efficiency ratio were also similar, according to data presented in Table 1.

Table 2 shows the results of the weight of retroperitoneal and periepididymal fat, and the sum of these two fat depots. There were significant differences in weight of retroperitoneal fat when assessed in isolation treatment (SCo versus STr) and training (SCo versus TCo) and also, when the training and treatment were associated (SCo versus TTr). With respect to fat periepididymal deposition, only the association of training with the treatment

(SCo versus TTr) was effective in significantly reducing the observed values. Evaluating the sum of the retroperitoneal and periepididymal fat, both control and treated rats submitted to exercise and drug treatment had a significant reduction in adiposity, although the treatment alone did not show this effect.

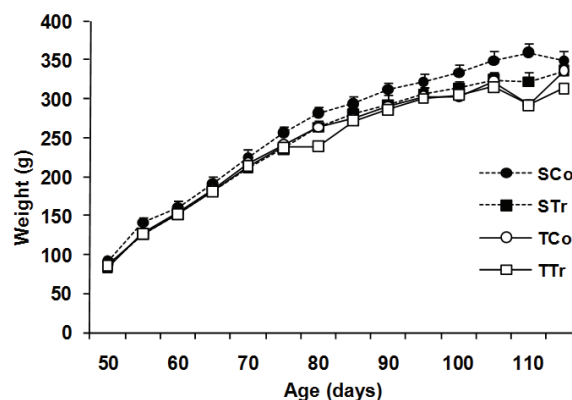


Figure 1. Effect of nandrolone decanoate in the evolution of body weight (g) of sedentary and trained rats. SCo: sedentary control; STr: Sedentary treated; TCo: trained control; TTr: trained treated. Values expressed in mean $\pm$ SEM, $n = 6$ animals per group.

Table 1. Initial weight (g), final weight (g), body weight gain (g), Lee's index, food intake (g day⁻¹) and food coefficient of efficiency (FCE) of rats trained and untrained, control and treated with nandrolone decanoate.

Parameters	SCo	STr	TCo	TTr
Initial weight	91.17 $\pm$ 4.70	84.14 $\pm$ 3.65	82.80 $\pm$ 2.49	85.67 $\pm$ 3.91
Final weight	348.25 $\pm$ 12.11	335.50 $\pm$ 12.16	335.90 $\pm$ 13.98	313.17 $\pm$ 10.13
Lee's index	28.14 $\pm$ 0.17	27.94 $\pm$ 0.38	28.00 $\pm$ 0.26	27.66 $\pm$ 0.16
Food intake	25.77 $\pm$ 0.92	24.71 $\pm$ 1.10	25.09 $\pm$ 1.22	23.79 $\pm$ 0.63
FCE	9.98 $\pm$ 0.38	10.17 $\pm$ 0.44	10.09 $\pm$ 0.60	9.56 $\pm$ 0.36

SCo: sedentary control; STr: Sedentary treated; TCo: trained control; TTr: trained treated. Values expressed in mean $\pm$ SEM; $n = 6$ animals per experimental group; means of groups did not differ significantly; $p < 0.05$ (ANOVA); IL (Lee's index = cube root of body weight per naso-anal length); FCE (food coefficient of efficiency) = daily weight gain divided by daily food intake.

Table 2 also presents the diameter of periepididymal adipocytes, cellularity and the correlation between the size of adipocytes and weight of fat deposition. The animals submitted to treatment with nandrolone associated with physical training had significantly smaller adipocytes in relation to other groups.

Table 2. Effect of treatment with nandrolone decanoate on the weight of retroperitoneal fat and periepididymal fat (g 100 g⁻¹ b w.), diameter of periepididymal adipocytes (μ m), cellularity and correlation index (R) between the diameter of adipocytes and periepididymal fat weight in sedentary rats and rats submitted to physical training.

Parameters	SCo	STr	TCo	TTr
Retroperitoneal fat	1.04 $\pm$ 0.10a	0.61 $\pm$ 0.06b	0.48 $\pm$ 0.08b	0.60 $\pm$ 0.09b
Periepididymal fat	0.78 $\pm$ 0.08a	0.69 $\pm$ 0.04ab	0.60 $\pm$ 0.06ab	0.53 $\pm$ 0.06b
Retroperitoneal + Periepididymal fat	1.82 $\pm$ 0.17a	1.31 $\pm$ 0.09ab	1.08 $\pm$ 0.14b	1.13 $\pm$ 0.13b
Diameter of adipocytes	81.28 $\pm$ 4.84a	76.53 $\pm$ 2.26a	72.04 $\pm$ 3.44ab	60.96 $\pm$ 2.29b
Cellularity	11.1141 $\times 10^9 \pm 1.6172 \times 10^9$ a	11.0394 $\times 10^9 \pm 0.5031 \times 10^9$ a	11.2883 $\times 10^9 \pm 0.5648 \times 10^9$ a	15.7572 $\times 10^9 \pm 1.8106 \times 10^9$ a
Correlation index (R)	0.83 (P = 0.04)	0.89 (P = 0.006)	0.94 (P = 0.01)	0.50 (P = 0.31)

SCo: sedentary control; STr: sedentary treated; TCo: trained control; TTr: trained treated. Values expressed in mean $\pm$ SEM; $n = 6$ animals per experimental group; means followed by different letters differ significantly; $p < 0.05$ (ANOVA); R = Pearson's correlation index.

The number of fat cells per gram of tissue did not differ significantly between the four groups, but the analysis of correlation between cell size and weight on trained animals that received the anabolic steroid was the only one not significant, which demonstrates that the hypertrophy of fat cells had less impact on weight, when compared with animals of other experimental groups.

Several blood parameters were also evaluated, as listed the results in Table 3. Only the values of blood glucose and total cholesterol were statistically significant different between the experimental groups. The TTr group presented lower glucose than the SCo group. With respect to cholesterol values, statistically significant differences were found between the SCo versus STr and, as also between SCo versus TTr.

Table 3. Effect of treatment with nandrolone decanoate on plasma glucose (mg dL⁻¹), cholesterol (mg dL⁻¹), triglycerides (mg dL⁻¹), total protein (mg dL⁻¹) and albumin (mg dL⁻¹) of sedentary rats and rats subjected to physical training.

Parameters	SCo	STr	TCo	TTr
Glucose	118.81 ± 3.45a	115.20 ± 2.21ab	116.96 ± 3.38ab	102.03 ± 6.45b
Cholesterol	121.58 ± 3.48a	93.61 ± 3.48b	102.74 ± 9.05ab	90.50 ± 4.90b
Triglycerides	103.17 ± 8.60a	114.86 ± 14.51a	119.40 ± 10.93 ^a	118.30 ± 9.74a
Total protein	55.35 ± 0.79a	53.06 ± 2.46a	51.92 ± 2.37 ^a	48.49 ± 2.32a
Albumin	2.10 ± 0.07a	1.88 ± 0.08a	1.81 ± 0.08 ^a	2.00 ± 0.06a

SCo: sedentary control; STr: sedentary treated; TCo: trained control; TTr: trained treated. Values expressed in mean ± SEM; n = 6 animals per experimental group; means followed by different letters differ significantly; p < 0.05 (ANOVA).

The Table 4 shows the weight of the heart, liver and kidneys calculated for 100 g of body weight. It appears that exercise training did not cause any significant effect on the weight of the organs, but the animals treated with nandrolone, both sedentary and trained, had heavier kidneys.

Table 4. Effect of treatment with nandrolone decanoate in weight of heart, liver and kidneys, of sedentary rats and rats submitted to physical training (expressed in gram per 100 g b.w.).

Organs	SCo	STr	TCo	TTr
Heart	0.34 ± 0.01a	0.35 ± 0.01a	0.29 ± 0.07a	0.35 ± 0.01 ^a
Liver	3.38 ± 0.07a	3.38 ± 0.13a	3.84 ± 0.11a	3.65 ± 0.13 ^a
Kidneys	0.72 ± 0.02a	0.82 ± 0.03bc	0.75 ± 0.02ab	0.86 ± 0.01c

SCo: sedentary control; STr: sedentary treated; TCo: trained control; TTr: trained treated. Values expressed in mean ± SEM; n = 6 animals per experimental group; means followed by different letters differ significantly; p < 0.05 (ANOVA).

Discussion

The use of AAS by athletes or recreation users have always been associated to the fact that these compounds are able to cause an evident change in body weight composition, stimulating a considerable increase in muscle mass. However, few studies have addressed the effects of the drugs on body fat distribution in human or animal models.

In our study, the final body weight fell slightly when analyzing exercise training with drug action, but we suppose it would become more pronounced if the observation period had been longer, since other studies conducted in rats submitted to swimming training for 6 weeks (CUNHA et al., 2005) or treadmill running for 8 weeks, also showed a discrete change in body weight. However, longer periods of training resulted in significant reductions in body weight gain, both in humans and in rats (KRAUS et al., 2002; PINTO et al., 2003).

Androgenic anabolic steroids (AAS) are able to induce numerous metabolic adaptations in rats, including decreased appetite, with consequent reductions in body weight gain (YU-YAHIRO et al., 1989). In our work, however, mean food intake and the coefficient of feed efficiency did not differ significantly among all the groups studied.

The presence of important anabolic effects on lean body mass has been reported (MULLIGAN et al., 2005; ALLOUH; ROSSER, 2010), but the effects of anabolic steroids on adipose tissue remain unclear. Peres and Luciano (1995) found an increase in adiposity in sedentary and trained animals treated with nandrolone decanoate, attributing it to an increase of fat weight gain that occurred in animals trained and treated. The results of this study showed that treatment with AAS caused reduction in retroperitoneal adipose tissue in sedentary rats, which remained unchanged in trained rats. The absence of any AAS effect was also evidenced on the weight of the periepididymal pad in both sedentary and trained groups. Our data showed that exercise seems to be more effective at reducing the amount of fat stored than when associated to AAS use. The hypotrophy in fat cells occurred only in the group of trained rats treated with nandrolone decanoate, exposing a synergistic effect of exercise and nandrolone decanoate. In three of four of our experimental groups significant positive correlations were found between adipocyte size and weight of the periepididymal depot, suggesting that animals of such groups had a hypertrophy, which is a determining factor to the weight of fat depots. Only the trained group treated with AAS the correlation was not observed. Whereas the increase in body fat may occur by both hypertrophy and hyperplasia, the data suggest the hypothesis that physical exercise associated with the use of anabolic steroids can cause an increase in the number of fat cells. If this hypothesis is correct, it is possible that the interruption of the treatment, training or both, may lead to an increase of the adipose tissue stores. Further studies of the effects of nandrolone decanoate on adipose tissue are needed, especially to investigate the hyperplasia of fat cells.

The reduction of adiposity that occur in TTr group may have favorably reflected on blood glucose and plasma levels of total cholesterol, as in this experimental group the mean values for these two metabolic parameters were significantly lower than in the SCo group. Other studies, however, did not find differences in serum glucose between the treated and control groups (PERES; LUCIANO, 1995).

Although some studies have shown deleterious effects of the use of AAS on the liver (VIEIRA et al., 2008), we did not find any significant differences in liver weight, in serum albumin concentration and in the total serum protein. Our data is in agreement with Peres and Luciano (1995) who have not reported any side effect. The weight of the kidneys, however, was significantly greater in animals treated with anabolic steroids, both sedentary and trained groups, which is consistent with the results observed by Hoseini et al. (2009) that found increased volume of the renal cortex of mice treated with nandrolone decanoate.

In this study we did not perform any behavioral test, but we observe that animals treated with nandrolone decanoate showed hostility, with a certain aggressiveness and irritability, as compared with the control animals. Pope-Júnior et al. (2000) and Takahashi et al. (2004) observed this behavior in studies of human.

Conclusion

The use of nandrolone decanoate associated to physical training was effective to lower retroperitoneal and periepydidimal fat depot final weight and adipocyte diameter. It also was effective to reduce glucose and cholesterol plasma levels. On the other hand, AAS increased kidney weight and elicited an aggressive behavior in all groups.

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