Acta Scientiarum

http://www.uem.br/acta
ISSN printed: 1679-9283
ISSN on-line: 1807-863X
Doi: 10.4025/actascibiolsci.v35i2.15513

Use of the anabolic steroid nandrolone decanoate associated to strength training in Wistar rats

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ABSTRACT. Anabolic steroids have been constantly used among athletes and physically active individuals. Adverse effects of such use are reported in the literature. However, little is known about the effects of anabolic steroid use associated with strength training. Thus, this research aimed to identify possible morphophysiological alterations in Wistar rats treated with the anabolic steroid nandrolone decanoate and submitted to strength training. Twenty Wistar rats were divided in four groups: sedentary control (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH). After the experimental protocol period, animals were killed and body weight, adiposity, renal and hepatic injury markers, plasmatic lipid profile, glycemia, and insulinemia were determined. The experimental conditions strength training and nandrolone decanoate (isolated or associated) were positively correlated to a reduction on visceral and subcutaneous adipose tissue. The association of strength training with nandrolone decanoate was the most effective condition to increase muscle mass. Heart and kidneys weights, aspartate aminotransferase (AST) and high density lipoprotein (HDL) concentration were also negatively modified. The data demonstrated effects of anabolic steroids in body composition, with better results when associated with strength training, but collateral effects were observed.

Keywords: anabolic steroids, nandrolone decanoate, strength training.

Uso do esteróide anabólico decanoato de nandrolona associado ao treinamento de força em ratos Wistar

RESUMO. Os esteróides anabólicos são usados indiscriminadamente entre atletas e praticantes de atividades físicas sendo que os efeitos adversos desse uso constam na literatura. Contudo, pouco se sabe dos efeitos do uso de esteróides anabólicos associados ao treinamento de força. Assim, este estudo objetivou identificar possíveis alterações morfofisiológicas em ratos Wistar tratados com decanoato de nandrolona e submetidos ao treinamento de força. Para atingir tal propósito, vinte ratos Wistar foram divididos em quatro grupos: sedentário controle (SC), sedentário hormônio (SH), treinado controle (TC) e treinado hormônio (TH). Após o período experimental, foram analisados o peso corporal, a adiposidade, marcadores de lesões hepáticas e renais, o perfil lipídico, a glicemia e a insulinemia. Foram observados efeitos do treinamento de força e do uso de decanoato de nandrolona (isolados ou associados) nos tecidos adiposos viscerais e subcutâneo. A associação de treinamento de força e uso de decanoato de nandrolona foi mais efetiva para aumentar a massa muscular. Os pesos dos rins e coração, e concentrações de aspartato aminotransferase (AST) e lipoproteína de alta densidade (HDL) foram negativamente modificados. Os dados demonstram efeitos do esteróide anabólico sobre a composição corporal, com melhores resultados obtidos com a associação ao treinamento de força, contudo efeitos colaterais foram observados.

Palavras-chave: anabolizantes, decanoato de nandrolona, treinamento de força.

Introduction

Steroid hormones are derived from cholesterol and metabolic precursors produced by the adrenal cortex and gonads (HÄKKINEN et al., 2001). Belonging to this class of hormone is testosterone, a molecule with anabolic and androgenic properties, which has also been synthetically produced and used for medical therapy (HANDELSMAN, 2001). From a historical perspective, german soldiers in World War II did the first non-medical use of anabolic steroids in order to boost aggression (FULLER, 1993). It was later discovered that these substances

could facilitate the growth of skeletal muscle in laboratory animals, leading to the abusive use of these compounds (NIDA, 2007).

Currently, the non-medical use of anabolic steroids has reached alarming proportions, affecting other population segments, as health club users and even high school students (MAHARAJ et al., 2000; YESALIS; BAHRKE, 2000). It is estimated that 3% of young population in United States have already used steroids, and about 3.5 million Americans were users of anabolic steroids (EKLÖF et al., 2003). In Brazil, the percentage of anabolic steroid users on school is about 2% (VENÂNCIO et al., 2010).

The use of steroids usually occurs in supraphysiological doses, and the dose used associated or not to exercise, is approximately forty times more than the baseline and twenty times the therapeutic use (EVANS, 2004). This abuse has resulted in liver (SCHUMACHER et al., 1999), kidney (YOSHIDA et al., 1994), and coronary problems (DO CARMO et al., 2011; FERRERA et al., 1997), psychological disorders (COWART, 1987; SU et al., 1993), hair and clitoris growth, menstrual disorders and male voice in women (STRAUSS et al., 1985), and gynecomastia, acne and baldness in men (PARKINSON; EVANS, 2006; HARTGENS; KUIPERS, 2004).

According to the National Institute on Drug Abuse (NIDA, 2000), nandrolone is one of the most used anabolic derivative of testosterone, because of its moderate androgenic potential associated with the good anabolic properties. Furthermore, the use of nandrolone decanoate has been applied for therapeutic purposes, and has been effective, for example, to reduce loss of body mass and muscle in HIV patients (SAHA et al., 2009), increase the number of satellite cells per muscle fiber (ALLOUH; ROSSER, 2010) and control of refractory anemia (CHAWLA et al., 2009).

In contrast, the deleterious effects of nandrolone decanoate improper use have also been found. Shokri et al. (2010) reported that physical training associated to the nandrolone decanoate utilization for eight weeks has affected fertility of rats, as well as generate testicular atrophy. Additionally, the use for a long period (more than three months) of nandrolone decanoate may affect the cardiovascular system by decreasing the myocardial contractile capacity (NORTON et al., 2000), as well as generate increased left ventricular wall (WOODIWISS et al., 2000) and ventricular morphological changes (MEDEI et al., 2010). In addition, Fineschi et al. (2011) showed that decanoate supplementation associated to physical exercise, for 42 days caused body weight gain and a raise in total cholesterol. In addition to, they also observed a moderate increase on heart weight, cardiac hypertrophy and evidence of myocardial lesions.

However, animal model research that combined exercise and anabolic steroids have adopted the aerobic or anaerobic exercise on treadmill or water (GEORGIEVA; BOYADJIEV, 2004). Using the apparatus proposed by Tamaki et al. (1992), which allows animals to reproduce the squat weight-lifting training, we proposed to analyze the supraphysiological effects of nandrolone decanoate use in association to strength training on body composition, lipid and glucose homeostasis, liver and renal injury markers and strength gain in adult male rats.

Material and methods

Animals and experimental procedures

The sample consisted of 20 male 4-month-old Wistar rats that were provided by the Central Animal Facilities, State University of Maringá. They were given a balanced diet and water *ad libitum*, kept on light/dark cycle of 12/12h. The animals were randomly divided into four groups: (1) sedentary control (SC); (2) sedentary hormone, treated with nandrolone decanoate (SH); (3) trained control (TC); (4) trained hormone, treated with nandrolone decanoate (TH).

The entire experimental protocol that involved the use of animals was approved by the Ethics Committee for Animal Research at the State University of Maringá, and was conducted in accordance with the institutional and national guidelines for the care and use of animals (028/2011).

Anabolic steroid

The SH and TH groups received intramuscular nandrolone decanoate (Deca-Durabolin®; Organon of Brazil LTDA, São Paulo State, Brazil) in a dose of 10 mg kg^{-1} $week^{-1}$ (two applications 5 mg kg^{-1} $week^{-1}$) during 4 weeks. The weekly dose used in the study protocol was similar to that used in earlier researches (NORTON et al., 2000; TRIFUNOVIC et al., 1995; WOODIWISS et al., 2000), and it is equivalent to the rates of abuse often applied by athletes.

Strength exercise training

For the strength exercise protocol, a squat apparatus was made and adapted from the model proposed by Tamaki et al. (1992), which simulated

the execution of the squat. The animals were submitted to one week of adaptation to the apparatus. Subsequently, after the stimulus, the training load (1 maximum repetition - MR) was used to the measure whether the rats could perform the correct movement, defined as the minimum load lifted. During the test, the rats performed no more than five attempts in order to estimate the maximum load completely suspended.

After determination of the maximum load, the training load was set to 75% of 1MR. The 1MR was measured fortnightly. The group TC and TH held three sets of 10 repetitions with 1 minute of rest between each set, three times a week for a period of 4 weeks.

Tissue harvesting procedures

After the experimental procedure, the animals were anesthetized with sodium pentobarbital (Hypinol® 3%, 4 mg 100 g^{-1} of body weight, intraperitoneally), and laparotomy was carried out to collect blood (4 mL) from the vena cava and to remove the tissues (heart, kidney, spleen, liver, seminal vesicles, adrenal gland, testicle, epididymal, retroperitoneal, subcutaneous and brown adipose tissues, and the soleus and gastrocnemius muscles) that were weighed and stored in a freezer at -80ºC.

Biochemical analysis

The plasma was stored in eppendorf tubes and frozen at -80ºC to subsequent analysis. The determination of the plasma concentration of triglycerides, total cholesterol, high density lipoprotein (HDL), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and glucose was conducted using the colorimetric method (Gold Analiza®, Belo Horizonte, Minas Gerais State, Brazil). Plasma insulin was determined by radioimmunoassay (RIA).

Statistical analysis

Statistical evaluation of results was performed by two-way analysis of variance with Newman-Keuls multiple comparison as a post-test, prefixing the level of significance at 5% ($p < 0.05$). Statistical tests were performed using the Prism v.2.1 (GraphPad®, USA) and Microsoft Excel® programs.

Results

Body mass, fat and fat free mass

Neither the administration of nandrolone decanoate and/or resistance exercise training for a period of 4 weeks resulted in significant differences in body weight (Table 1).

Table 1. Body weight, initial and final fat weight (g), periepididymal, retroperitoneal and subcutaneous tissue ($g.100g^{-1}$ body weight) and food intake ($g.day^{-1}$ $animal^{-1}$) of sedentary control (SC), sedentary hormone (SH) trained control (TC) and trained hormone (TH) groups. Values are represented as mean ± SEM.

	SC	SH	TC	TH
Initial body weight (g)	411.5 ± 9.5	431.4 ± 16.8	406.6 ± 17.8	415.6 ± 21.0
Final body weight (g)	450.2 ± 11.5	451.0 ± 24.2	432.6 ± 21.1	431.5 ± 22.6
Retroperitoneal adipose tissue	2.07 ± 0.16	1.41 ± 0.23*	1.46 ± 0.11*	1.28 ± 0.20*
Periepididymal adipose tissue	1.90 ± 0.13	1.31 ± 0.21*	1.21 ± 0.15*	1.34 ± 0.17*
Subcutaneous adipose tissue	2.01 ± 0.20	0.74 ± 0.07*	0.61 ± 0.11*	0.72 ± 0.10*
Food consumption	28.6 ± 2.2	26.0 ± 0.04	24.5 ± 0.8	27.9 ± 0.5

*$p < 0.05$ compared to SC group.

With regard to body adiposity, the effects of strength training and administration of nandrolone decanoate were observed on the visceral and subcutaneous depots of adipose tissue. Significant differences were seen between the groups SH, TC and TH compared to the SC group ($p < 0.05$). However, the association between strength training and administration of nandrolone decanoate did not cause an accumulative effect (Table 1). The food consumption did not change between groups.

To identify the influence of the experimental protocol on fat free mass, we analyzed two different muscles: soleous (Figure 1A) and gastrocnemius (Figure 1B). There were no influences on soleous muscle mass (which features a large formation of oxidative fibers) among the groups, except a tendency in TH group (SC vs. TH, $p = 0.069$). In relationship to gastrocnemius muscle mass (which has a higher content of glycolytic fibers when compared to soleus muscle), we observed a pronounced effect of strength training, with the trained groups (TC and TH groups) presenting an increased gastrocnemius muscle mass in comparison to the sedentary groups (SC and SH groups, $p < 0.05$). The isolated action of nandrolone was not observed, as noted by the absence of significant difference between groups SC vs. SH and TC vs. TH.

Tissue weight

Table 2 presents the response of different tissues to strength training and administration of nandrolone decanoate. The TH group presented a heart weight statistically higher than SC group $p < 0.05$). In addition, the administration of nandrolone decanoate led to an increase in kidney mass, regardless of the realization of strength training (SH and TH vs. SC and TC, $p < 0.05$). In the absence of strength training, administration of

nandrolone decanoate caused a reduction in brown adipose tissue (SH vs. SC, $p < 0.05$). The weight of the remaining tissues did not present any differences.

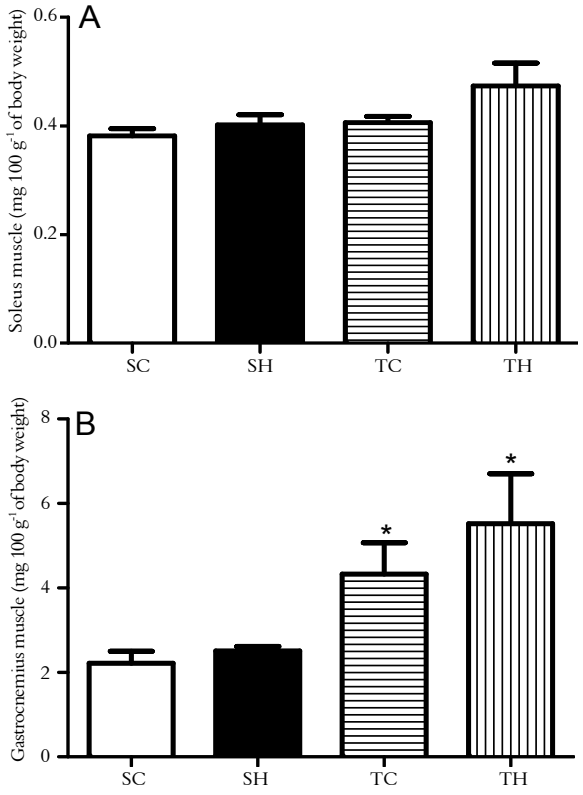

Figure 1. (A) Soleus muscle weight (mg.100g^{-1} body weight) and (B) gastrocnemius muscle (mg 100 g^{-1} body weight) of sedentary control (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH) groups. *$p < 0.05$ compared to group SC and SH. Values are represented as mean ± SEM.

Table 2. Weight of different tissues (g 100 g^{-1} body weight) of sedentary control (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH) rats. Values are represented as mean ± SEM.

	SC	SH	TC	TH
Heart	0.37 ± 0.01	0.39 ± 0.01	0.40 ± 0.01	0.44 ± 0.01*
Kidney	0.54 ± 0.02	0.67 ± 0.01#	0.57 ± 0.03	0.67 ± 0.03#
Spleen	0.15 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.15 ± 0.01
Liver	2.75 ± 0.15	2.82 ± 0.15	2.93 ± 0.05	2.92 ± 0.09
Seminal vesicle	0.53 ± 0.05	0.48± 0.07	0.49 ± 0.03	0.57 ± 0.02
Adrenal glands	0.013 ± 0.001	0.011 ± 0.001	0.013 ± 0.001	0.012 ± 0.001
Testicle	0.68 ± 0.02	0.72 ± 0.03	0.76 ± 0.03	0.72± 0.04
Brown adipose tissue	0.13 ± 0.01	0.05 ± 0.01*	0.11 ± 0.02	0.10 ± 0.01

*$p < 0.05$ compared to SC group; # $p < 0.05$ compared to SC and TC groups.

Markers of kidney and liver damage

The association between the use of anabolic steroids with renal and hepatic lesions, led us to perform the analysis of plasma markers to detect any potential harmful effect of nandrolone decanoate. Despite the increase in kidney mass after the administration of nandrolone decanoate, there were no changes in creatinine plasma levels (Table 3), which is a parameter used to identify modifications in glomerular filtration. However, when we determined the concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) the SH group showed higher levels of AST in comparison to the other groups but no changes in ALT concentration (Table 3).

Table 3. Creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of sedentary control rats (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH). Values are expressed as mean ± SEM.

	SC	SH	TC	TH
Creatinine	1.09 ± 0.04	0.96 ± 0.06	0.87 ± 0.03	1.07 ± 0.08
AST	27.76 ± 1.10	35.85 ± 3.01*	24.25 ± 0.80	24.33 ± 1.90
ALT	33.99 ± 1.24	42.03 ± 2.86	36.51 ± 0.83	39.97 ± 2.26

*$p < 0.05$ compared to other groups.

Lipid profile and glycemic control

The plasma lipid profile was also measured in our study (Table 4). There were no significant differences in the levels of total cholesterol and triglycerides, but there was a significant reduction in HDL cholesterol in the SH group compared to other groups.

Table 4. Plasma lipid profile of sedentary control (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH) rats. Values are expressed as mean ± SEM.

	SC	SH	TC	TH
Total cholesterol	73.30 ± 6.12	57.38 ± 1.11	68.63 ± 1.73	64.26 ± 3.92
HDL cholesterol	49.60 ± 1.98	41.70 ± 1.45*	53.38 ± 3.44	51.70 ± 3.15
Triglycerides	56.80 ± 5.08	38.10 ± 9.24	58.25 ± 7.60	46.90 ± 12.74

*$p < 0.05$ compared to other groups.

Additionally, we also determined glucose plasma levels. The TC group presented lower blood glucose (Figure 2A). However, neither the administration of anabolic steroid nor the resistance physical training led to changes in insulin levels (Figure 2B) and HOMA index (Figure 2C).

Development of muscle strength

The development of muscular strength is associated with an increase in muscle area and steroid use (SCHROEDER et al., 2003). In order to measure this muscular capacity we performed the test of one maximum repetition throughout the experimental protocol. During the 4 weeks of strength training, there were no significant differences in muscle strength gain (Figure 3) between the trained groups (TC vs. TH).

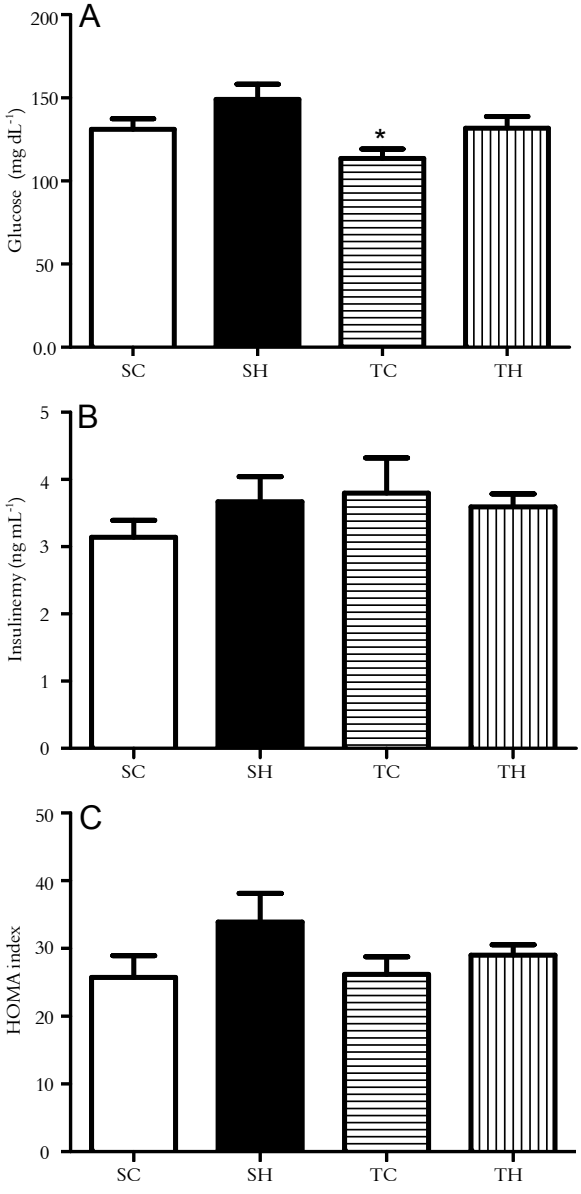

Figure 2. (A) Glucose, (B) insulin and (C) HOMA index of sedentary control rats (SC), sedentary hormone (SH), trained control (TC) and trained hormone (TH). Values are expressed as mean ± SEM. *p < 0.05 compared to SH.

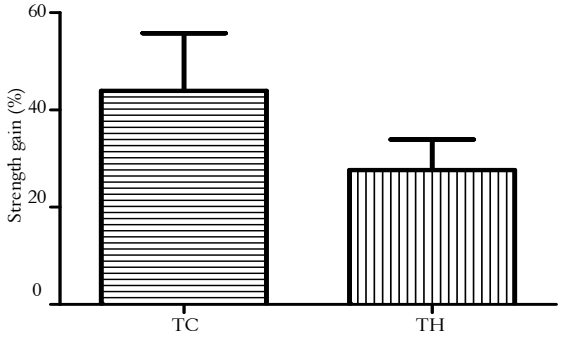

Figure 3. Gain muscle strength after 4 weeks of resistance exercise training.
Values are represented as mean ± SEM.

Discussion

The use of anabolic steroids is very common in sports, whether in the professional or amateur situations. Among the various anabolic steroids available, nandrolone decanoate is presented as one of the most used, although in experimental procedures challenging to mimic the strength training adopted by gym athletes. With the squat apparatus utilized in our study, we tried to reproduce the experimental protocol training to a very common squat exercise performed in gyms.

Several studies have sought to study the therapeutic action of nandrolone decanoate aiding in the recovery of body weight of HIV infection (GOLD et al., 2006; SARDAR et al., 2010), cachexia (MUSCARITOLI et al., 2006) and hemodialysis patients (JOHANSEN et al., 2006). In contrast, the drug administration to rats or bodybuilders (HARTGENS et al., 2001) with no history of pre-existing condition that would lead to reduced body weight, the effects of nandrolone decanoate on body weight, apparently, are absent (FINESCHI et al., 2011). The same was observed in our study, in which body weight was not altered by administration of nandrolone decanoate. This influence was independent of the realization of strength training. Some studies show a decrease in body weight by the combination of exercise associated to the use of nandrolone decanoate (FINESCHI et al., 2011; ROCHA et al., 2007).

Regarding the adipose tissue, the administration of nandrolone decanoate caused a significant decrease in both visceral (epididymal and retroperitoneal) and subcutaneous fat depots. This is an interesting data since adipose tissue, in special visceral depots, are associated to the development of several metabolic diseases (WRONSKA, KMIEC, 2012). In this way, nandrolone decanoate and exercise alone reflected the same adiposity changes, with no addictive effects of their association. Is also important to highlight that we used data from visceral and subcutaneous fat depots due regional differences previously reported (PALOU et al., 2010; TCHOUKALOVA et al., 2010a and b; WRONSKA, KMIEC, 2012).

In a recent study, Alsiö et al. (2009) observed a dose-response effect of testosterone decanoate in gene expression of β-3 adrenergic receptors in visceral adipose tissue surrounding the adrenal gland of rats, which suggestive of an increased lipolytic activity in this tissue. Regarding the reduction of subcutaneous tissue, a dose-response study revealed that only when high doses (600 mg) were

administered there were reductions in body fat percentage of subjects, while lower doses (25 and 50 mg) led to an increase in fat mass (BHASIN et al., 2001). However, the dose and time used in our experiment led to reductions in both depots, indicating that additional studies are necessary to answer this question. In relationship to exercise and adiposity reduction, its beneficial effects were previously reported (ISMAIL et al., 2012).

Some studies have reported a more pronounced gain in muscular strength with the association between anabolic steroid with strength training (BHASIN et al., 2001; SCHROEDER et al., 2003; SCHROEDER et al., 2005), however we observed a lack of significant differences on this parameter, when comparing the groups TC and TH. We believe that this lack of difference may be due to differences in the drug action between the various anabolic steroids used in previous studies and due to the time involved in the experimental protocol, i.e., four weeks. We also observe an increase in the mass of the gastrocnemius muscle in the groups who performed strength training, regardless of the administration of nandrolone decanoate was identified. Nonetheless, we have not performed any additional experimental that could help us to explain the molecular mechanisms that may be involved in the effects of using nandrolone decanoate in combination or not with strength training on muscle mass hypertrophy.

The effect of anabolic steroid use on the cardiovascular system has been the reported by several studies. In our work we observed that the strength training associated to the administration of nandrolone promoted an increased in heart weight. Similar effects have been reported by Fineschi et al. (2011), which described that nandrolone supplementation associated with physical exercise, for 42 days led to moderate increase in heart weight, cardiac hypertrophy and evidence of myocardial lesions. In a research that aimed to establish if a single and high dose of nandrolone decanoate (20 mg kg^{-1}) could elicit anabolic effects on morphological parameters the authors observed an increase in heart weight after 10 days of steroid administration (TYLICKI et al., 2007). Medei et al. (2010) found cellular remodeling in both ventricles, together with electrical changes in the left ventricle towards the use of nandrolone decanoate super dose. It has also been pointed out that the use of the drug may generate an increase in left ventricular wall (WOODIWISS et al., 2000). Finally, Silva et al. (2010) observed ECG negative changes with 3 weeks of nandrolone use.

In relation to the weight of the kidneys, we found differences in the two groups that were treated with nandrolone. Hoseini et al. (2009) showed that animals treated with nandrolone had the kidney weight increased by about 30%. An attention should be given to this fact, since the outcomes of the use of anabolic steroids on kidney function in physically healthy individuals remain inconclusive.

No changes were found between groups with respect to the weight of spleen, liver, seminal vesicles, adrenal glands and testes. Nevertheless, the steroid administration had a negative impact on liver function, whereas in the SH group AST was found significantly higher compared to the others. Since elevated levels of serum transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may reflect secondary hepatic dysfunction when excessive doses of anabolic steroids are administered (PERTUSI et al., 2001), our result indicates that decanoate nandrolone use caused a negative effect on liver. Corroborating our findings, Vieira et al. (2008) showed that administration of nandrolone decanoate leads to a dose-dependent increase of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In addition, the authors demonstrate that administration of the drug in higher doses in clinics can be potentially harmful to the liver, leading to incipient fibrosis. It is noted that the TH group did not achieve such high indicators of liver injury. However, further analysis is needed to prove a possible cytoprotective effect of strength training.

In regard to glucose and lipid metabolism, our results were partially similar to that obtained by Venâncio et al. (2010). The authors reported a reduction on the levels of LDL, total cholesterol, HDL and triglycerides in individuals who have undergone resistance training and made use of steroids. Our data only observed a reduction in HDL cholesterol in the SH group. In this sense, a classic study conducted by Kirkland et al. (1987), with 57 boys in four developmental stages of puberty, through clinical examination, found that the increase in testosterone at puberty resulted in a decrease in HDL. However, when hypogonadism is induced experimentally through the administration of GnRH agonists or when the endogenous production of testosterone is inhibited an increase in HDL is elicited. Thus, we conclude that in most of the cases the use of anabolic steroids is capable to induce a decrease in HDL (DOBS et al., 2001). Additionally, strength training seems to promote a

liver protective effect by restoring ALT and AST values back to a normal range in TH group.

The present work also evaluated the beneficial effect of strength training on circulating levels of glucose and insulin. The TC group presented a lower fasting glycemia when compared to the others groups. Exercise has been shown to positively influence glucose homeostasis through increased glucose transport system on muscle and reduction of hormonal stimulus for production and release of hepatic glucose (HENRIKSEN, 2002).

Conclusion

This research points out to positive effects of administration of nandrolone decanoate, especially associated to strength training on body composition by act reducing visceral and subcutaneous adipose tissue. However, due no changes in muscle mass and strength, associate to changes in markers of renal and hepatic injury and the increase in heart weight, we forewarn the use of nandrolone decanoate except when clinically prescribed.

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Received on December 14 2011.
Accepted on April 10, 2012.