

Chronic Users of Supraphysiological Doses of Anabolic Androgenic Steroids Develop Hematological and Serum Lipoprotein Profiles That Are Characteristic of High Cardiovascular Risk

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Abstract

The purpose of this study was to evaluate the effect of long-term anabolic androgenic steroids (AAS) use on the hematological and lipoprotein profile of young men practicing sports at fitness centers. Twenty-two male subjects were divided in two groups: AAS (n = 11; 27.3 ± 4.5 years; 85.1 ± 6.8 kg; 174 ± 5.5 cm) and control (n = 11; 24.7 ± 3.6 years; 81.7 ± 7.6 kg; 178.5 ± 6.5 cm). The hemodynamic response, metabolic profile (blood glucose and lactate) and serum lipoprotein levels were measured prior to, during, and after a submaximal exercise test on a cycloergometer. Blood samples were obtained before the exercise test to determine the hematological profile (white and red cells). The hemodynamic response showed no statistically difference between groups before, during, or after submaximal exercise test. Hemoglobin, hematocrit, erythrocytes, leucocytes and monocytes were significantly higher (p < 0.05) in AAS users compared to control subjects. HDL-cholesterol level was significantly lower, whereas triglycerides levels, LDL-cholesterol level and the LDL-c/HDL-c ratio were significantly higher in the AAS group. Blood glucose and lactate levels were significantly higher in the AAS users after submaximal exercise test. In conclusion, young men practicing sports at fitness centers who are AAS users exhibit proatherogenic and prothrombotic profile, and premature metabolic disturb in despite of regular physical activity.

Keywords: Anabolic androgenic steroids, Atherogenesis, Lipoprotein, Submaximal exercise test

Introduction

Anabolic androgenic steroids (AAS) are analogs of testosterone that have been synthesized with the goals of maximize maximizing its anabolic effects and reduce reducing its androgenicity [1,2]. The clinical applications of AAS include the therapy of gonadal dysfunction and muscle-wasting disorders, catabolic states, osteoporosis, starvation and burns [3,4]. However, AAS abuse has adverse effects and may cause morbidity and mortality [3,4,5]. The self-administration of high doses of AAS is widespread among young athletes and non-athletes aiming to optimize strength

and muscle mass gain [3]. AAS abuse is increasing, particularly at fitness centers, in recreational athletes who seek to improve their physical aesthetic appearance [3].

Among the many toxic and hormonal effects of AAS that have been documented, attention has been turned recently to the increased levels of total cholesterol and low-density lipoprotein (LDL-cholesterol), and decreased levels of high-density lipoprotein (HDL-cholesterol) [3,6,7]. Supraphysiological doses of AAS elevate platelet aggregation, enhancing monocyte adhesion and macrophage lipid loading [8]. These changes in hematological and lipoprotein profiles induced by high doses of AAS have been associated with cardiovascular risk because an increase in serum LDL-cholesterol promotes its binding to connective tissue of the arterial intima, where it is oxidized by monocytes/macrophages [9,10]. However, it is not clear whether this response depends on the AAS dose or on the

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timing of repeated doses. In addition, it is unclear whether there is a change in the lipoprotein profile after submaximal exercise in those who use high doses of AAS. On the other hand, some studies comment that submaximal exercise induces an increase in hepatic lipoprotein lipase, which in turn leads to enhanced triglyceride clearance and probably decreases plasma clearance of HDL constituents [11].

These alterations in the lipoprotein profile by AAS can induce arterial hypertension and peripheral arterial resistance [12,13]. Thus, androgens might thereby initiate or potentiate hypertension and hemodynamic alterations by stimulating tissues distal to the myocardium [14]. Controversy also exists on the action of AAS on blood pressure. Some investigators have observed increased blood pressure in weight lifters using anabolic steroids [10,12]; whereas, others have not [15,16]. Other studies have indicated that AAS can cause not only hypertension, but also impaired vascular reactivity, metabolic disorders, and cardiac lesions [7,14,17].

The purpose of this study was to evaluate the effect of long-term AAS use on the serum lipoproteins levels, hematological profile, hemodynamic and metabolic response at rest and after submaximal exercise test in young men practicing sports at fitness centers.

Methods

Approach to the Problem

This study evaluated specifically the hemodynamic and metabolic response of long-term AAS, to a submaximal exercise protocol testing.

Subjects

Twenty-two subjects were recruited from various fitness centers in Rio de Janeiro (Rio de Janeiro, Brazil). All subjects signed an informed consent and completed an 18-question survey [18]. Anonymity was expressly guaranteed. All subjects were considered healthy on the basis of history, physical examination and normal resting electrocardiogram. They were adult male subjects regularly engaged in strength training (mean = 6 dayweek⁻¹) and low-level aerobic training (mean = 2 dayweek⁻¹). All subjects were non-smokers, non-alcohol users, and non-illicit drug users (cocaine, marijuana, and heroin). Exclusion criteria were refusal to participate in the research, atrial fibrillation, significant valvular heart disease, coronary artery disease, systemic hypertension (≥ 140 mmHg for systolic pressure and ≥ 90 mmHg for diastolic pressure or use of antihypertensive medication) and metabolic syndrome.

Based on the results of the screening questionnaire subjects were assigned to the AAS group (n = 11; age 27.3 \pm 4.5 years; weight 85.1 \pm 6.8 kg; height 174 \pm 5.5 cm; body mass index (BMI) – 28 \pm 2.5 kg/m²; body fat 11.3 \pm 2.8 %) or control group (n = 11; age 24.7 \pm 3.6 years; weight 81.7 \pm 7.6 kg; height 178.5 \pm 6.5 cm; BMI 25.6 \pm 1.7 kg/m²; body fat 15 \pm 6.2 %) groups. The control group had not utilized any type of anabolic-androgenic steroids or analogous compounds. Subjects in the AAS group were individuals who had been using anabolic steroids for at least five years with a current dosage of 410 \pm 79 mgweek⁻¹. The AAS administered by

intramuscular injections were nandrolone, stanozolol and different esters of testosterone. The substances taken orally included oxymetholone, stanozolol and fluoxymesterone.

Body weight was measured using a calibrated physician's beam scale (model 31, Filizola, São Paulo, Brazil), with the men dressed in shorts. Height was determined without shoes using a stadiometer (model 31, Filizola, São Paulo, Brazil) after a voluntary deep inspiration. Body-mass index (BMI) was calculated as body weight divided by squared height (kg/m²). Body fat percentage (%) was estimated using the seven-site skinfold procedures according to the guidelines of the American College of Sports Medicine [13]. No clinical problems occurred during the study.

AAS use by individuals of AAS group has been previously assessed indirectly by electrochemiluminescence determination of serum testosterone, FSH, LH, and estradiol [19]. The experimental protocol was in accordance with the declaration of Helsinki and the study protocol was approved by the Research Ethics Committee of the Fluminense Federal University.

Procedures

Submaximal Exercise Protocol

All testing was performed between 1:00 and 3:00 PM on a cycloergometer (Monark 828 E, Stockholm, Sweden) at submaximal workload using the *Astrand-Rhyming* protocol [20]. The test was preceded by a 3-min warm-up with a workload of 50 W and keeping pedal speed at 50 rpm. After warm-up the workload was maintained between 100 and 130 W until the heart rate (HR) reached a steady state level, usually 6 or 7 min (140-150 beats/min, with a difference of less than 5 beats/min between rates in the 5th and 6th minutes or the 6th and 7th minutes). Ambient temperature was 22 to 24 °C. The HR was continuously monitored during exercise using a 12-lead ECG monitor system (CONTEC, model 8000D, New York - USA). Subjects received a light lunch 2 hours before the test. Coffee, tea and alcohol intake was prohibited for 12 hours and subjects avoided formal and strenuous exercise for 48 hours before testing.

Prior to testing, cardiovascular variables were measured following a 10 minute supine rest. During the test, subjects were continuously monitored via 12-lead electrocardiogram (ECG). Blood pressure, both systolic (SBP) and diastolic (DBP), were measured at rest in the supine position (at least two measurements on both arms after 10 minutes in the supine position), at each step of exercise and after exercise in the first, second, and third minute by a measure based on the I and V Kortokoff sounds, respectively using a cuff specially adapted to the enlarged upper arm girth as needed. Mean arterial blood pressure (MBP) was calculated from Systolic (SBP) and diastolic (DBP) pressures using the equation: MBP = DBP + (SBP - DBP)/3. Blood pressure was measured on the left arm according to the auscultatory method with a mercury-column sphygmomanometer.

Testing was symptom limited and was terminated if subjects reported limiting symptoms of dyspnea, fatigue, and chest pain or for medical reasons including horizontal or

down-sloping ST-segment depression of ≥ 1 mm, ST segment elevation > 1 mm in nonQ wave lead, atrial fibrillation or supraventricular tachycardia, suggestive of the left bundle branch block, abnormal blood pressure response to exercise (blood pressure $\geq 220 \times 120$ mmHg), fall in systolic blood pressure (> 20 mm Hg), variation in diastolic pressure under stress higher than 15 mmHg, presyncope, severe arrhythmias, presence of extrasystoles, ataxia or ventricular ectopy (presence of 6 or more premature ventricular beats per minute in recovery) and development of bundle-branch block or Intraventricular Conduction Delay (IVCD) that cannot be distinguished from ventricular tachycardia [5,11].

Blood parameters

After an overnight fast, venous blood samples were taken from the right arm between 8 and 10 a.m. after 10 minutes of rest in a seated position. Blood was sampled from the antecubital vein into two tubes for each subject: In the first tube, containing 2.5 % EDTA, 5 ml of blood was collected for hematological examination and in the second tube, 5 ml was collected for measuring serum lipoprotein levels. Immediately after the recovery period following the submaximal exercise protocol (3 minutes), an additional 5 ml was collected for measuring serum lipoprotein levels. Samples were centrifuged at $1500 \times g$ for 10 minutes and the serum was separated into aliquots of $400 \mu\text{l}$ and quickly frozen and stored at -70°C for a maximum of 6 months.

Hemoglobin, erythrocytes, hematocrit, platelets, total blood leucocytes (white cells), lymphocytes and monocytes were analyzed on an automated cell counter [Cell-Dyn 3500

(Abbott Laboratories, Abbott Park, IL, USA)]. Clear serum was used for determination of total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations, which were analyzed using commercially available colorimetric enzymatic kits (Raichem, Columbia, MD). The blood glucose concentrations were measured at rest and after the end of the incremental exercise using a glucose analyzer (Glucose Meter Kit – Roche Bioelectronics, Basel, Switzerland).

Fingertip capillarized blood micro-samples were taken for blood lactate assessment at rest, after warm-up, during peak effort, and 3 minutes after the end of the incremental exercise. A lactate analyzer (Lactate Pro LT-1710, Roche Bioelectronics, Basel, Switzerland) was used.

Statistical Analysis

Data are expressed as mean \pm SEM. The level of significance was set at $p < 0.05$. Inter-group differences were calculated using two-way analysis of variance (ANOVA) with post-hoc comparisons (Bonferroni test) if the overall probability value was $p < 0.05$. Comparisons between groups (AAS and Control) for blood cells were based on Student's unpaired t test. The $\Delta\%$ was calculated from the difference between Control and AAS groups. All statistical analysis was performed using Graphpad Prism 5.0 (Graphpad Software Inc., San Diego CA, USA).

Results

Hemodynamic response and blood lactate

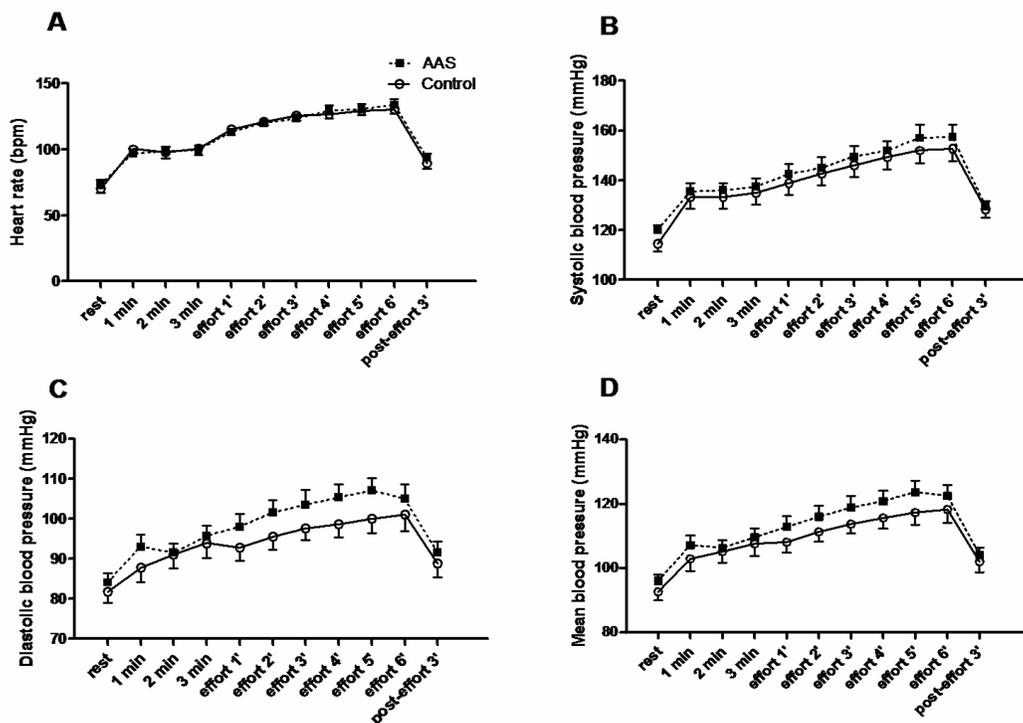


FIGURE 1 – Hemodynamic response in control and AAS groups at rest, during exercise and after 3 minutes of recovery.

No statistically significant differences between groups were observed for heart rate, systolic, diastolic or mean arterial pressure, at rest, during the exercise testing or post-effort (Figure 1). The workload at which subjects reached the steady-state HR during the submaximal exercise test was significantly greater ($p < 0.01$) in the Control group than in the AAS group (132.7 ± 5.4 watts and 113.6 ± 4.9 watts, respectively).

The mean values of blood lactate were similar in both

groups during rest and during submaximal exercise. However, in the AAS group lactate was significantly higher ($\Delta\% = 26.4\%$) after submaximal exercise when compared to control group (Figure 2A). The rest level of blood glucose were similar for both groups at rest, but after submaximal exercise it was significantly greater in the AAS group ($\Delta\% = 17.1\%$) than in the Control group (Figure 2B).

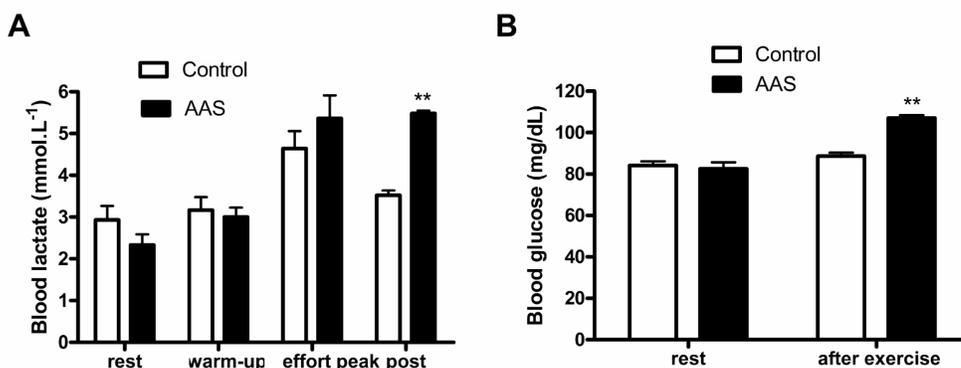


FIGURE 2 – Effects of chronic AAS use on blood lactate and glucose levels. **A**, lactate level at rest, warm-up (3 minutes), during the peak of submaximal exercise (effort peak), and 3 minutes after exercise (post). **B**, glucose level at rest and after submaximal exercise. Data were analyzed by ANOVA two-way with post-hoc comparisons (Bonferroni test). Values are expressed as mean \pm SEM. ** $P < 0.01$ compared to Control group.

Table 1. Baseline hematological parameters

	Control	AAS	P-value
Hemoglobin (g/dl)	14.1 \pm 0.3	15.4 \pm 0.2	0.002
Hematocrit (%)	43.3 \pm 0.7	45.3 \pm 0.5	0.020
Erythrocytes ($\times 10^6/\text{mm}^3$)	5.1 \pm 1.1	5.4 \pm 0.1	0.020
Platelets ($\times 10^3/\mu\text{l}$)	234 \pm 18	251 \pm 16	0.503
Leukocytes (cells/ μl)	5427 \pm 391	7045 \pm 553	0.020
Lymphocytes (%)	27.8 \pm 2.1	29.0 \pm 1.6	0.388
Monocytes (%)	6.3 \pm 0.6	8.9 \pm 0.6	0.006

Values are expressed as mean \pm SEM. n = 11 in each group. Data were analyzed by Student's unpaired *t* test.

Hematological results

AAS use induced a significant alteration in blood cell population (red and white cells). Significant differences were observed in hemoglobin ($\Delta\% = 9.4\%$), hematocrit ($\Delta\% = 4.8\%$), erythrocytes ($\Delta\% = 6.6\%$), leucocytes ($\Delta\% = 29.8\%$) and monocytes ($\Delta\% = 41.9\%$), which were all higher in the AAS group compared to Control group. Table 1 summarizes the hematological data for both groups.

Serum total cholesterol, triglycerides and lipoproteins

Figure 3 shows the lipidic profile of AAS users. The total cholesterol (TC) showed no significant difference between groups (Figure 3A). In contrast, serum triglycerides were

significantly higher ($\Delta\% = 32.6\%$) in the AAS group,

compared to Control group (Figure 3B). The AAS group showed a significant decrease ($\Delta\% = 29.8\%$) in HDL-cholesterol (Figure 3C) and a significant increase ($\Delta\% = 25.4\%$) in LDL-cholesterol (Figure 3D), when compared with the Control group. The TC/HDL-c ratio did not show a significant difference between groups (Figure 4A), but the LDL-c/HDL-c ratio (Figure 4B) was significantly greater in the AAS group ($\Delta\% = 53\%$).

Discussion

The purpose of this study was to evaluate alterations in blood characteristics of long-term AAS users practicing sports at fitness centers. Our data showed that these AAS users have higher serum LDL-cholesterol, lower HDL-cholesterol and

higher triglycerides levels, exhibiting a pro-atherogenic profile, despite regular physical activity. However, we did not observe any significant difference in the hemodynamic parameters between the groups. The similarity in the hemodynamic

responses in both groups indicated that a compensatory augmentation of regional flow to the exercising muscle may be existed to maintain regional microvascular perfusion [11,21].

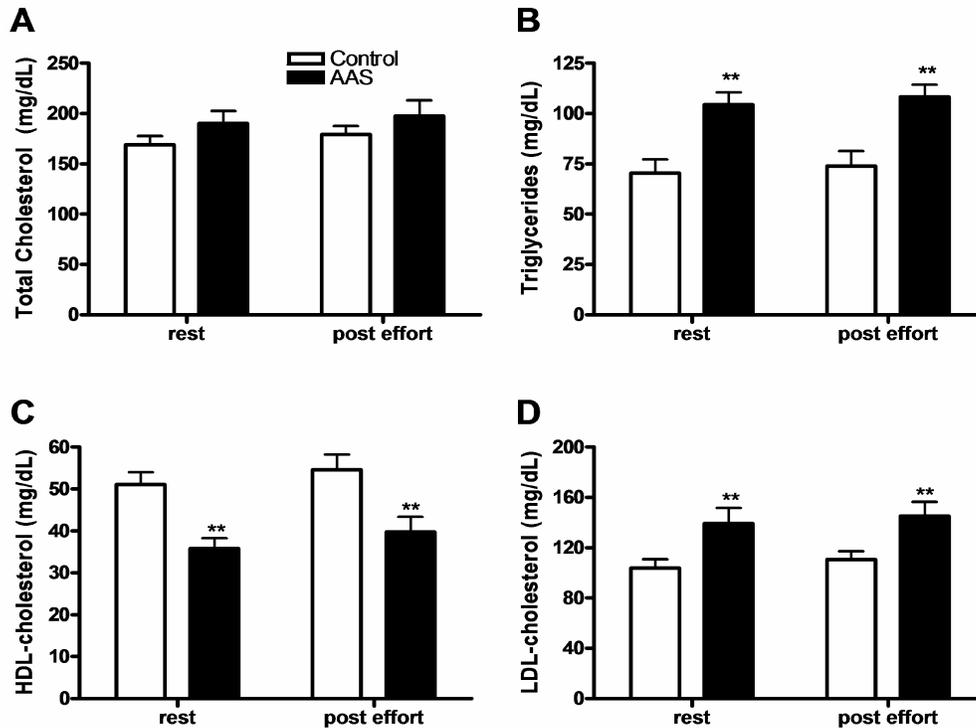


FIGURE 3 – Effects of chronic AAS use on serum lipoprotein levels. Plasma concentration of total cholesterol (A), triglycerides (B), HDL-cholesterol (C) and LDL-cholesterol (D). Data were analyzed by ANOVA two way with post-hoc comparisons (Bonferroni test). Values are expressed as mean ± SEM. ** P < 0.001 compared to Control group.

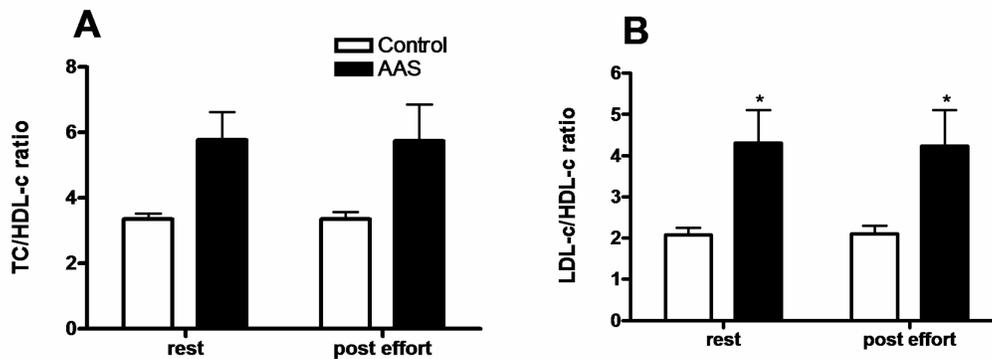


FIGURE 4 – Effects of chronic AAS use on TC/HDL-c (A) and LDL-c/HDL-c (B) ratios. TC: total cholesterol; HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein. Data were analyzed by ANOVA two way with post-hoc comparisons (Bonferroni test). Values are expressed as mean ± SEM. *P < 0.0001 compared to Control group.

These findings are consistent with previous reports examining the association between AAS use and lipoprotein profile in athletes [7,17,22]. The decreased HDL-cholesterol level in AAS users have been related to an AAS-induced increase in hepatic triglyceride lipase, which promotes selective hydrolysis of an subfraction (HDL₂) rather than

HDL₃ [15,23]. Thus, the low HDL-cholesterol and HDL₂ subfraction levels in AAS users are associated with pathogenesis of coronary atherosclerosis and higher risk for ischaemic heart disease by impairing the clearance of cholesterol from arterial walls [23]. Hence, the reduction in the plasmatic level of HDL-cholesterol is a well-known risk factor

for atherosclerotic cardiovascular disease [24].

The situation is worsened by AAS-induced elevation of plasma LDL-cholesterol concentration. LDL-c is a risk factor for coronary heart disease since the excess LDL-cholesterol may accumulate in artery walls resulting in atherosclerosis [10,25]. The LDL-c/HDL-c ratio has been proposed as a most reliable criterion for coronary heart disease risk [16,26]. In our study, the LDL-c/HDL-c ratio was significantly higher in the AAS group. Other studies have reported that testosterone enanthate increase in the LDL-c/HDL-c ratio in animal model [27] and human [28]. Few studies have utilized the LDL-c/HDL-c ratio for analysis of cardiovascular risk profile in AAS users, but it appears to be an excellent predictor of cardiovascular disease risk, and a high risk of death is associated with an LDL-c/HDL-c ratio between 3.7 and 4.3 [16]. Our AAS group had ratios in this range (at rest = 4.3, and post effort = 4.2).

A decrease in triglyceride concentration plays a major role in increasing HDL-cholesterol levels and regular exercise may be necessary to sustain the positive effects of exercise on lipid metabolism [21]. Some studies have shown that administration of stanozolol and mesterolone promotes high lipoprotein lipase concentrations, associated with a significant increase in blood triglyceride level [15,29]. This combination leads to an increase in the triglyceride and lipoprotein lipase concentrations, reflected in the conversion of VLDL-cholesterol to LDL-cholesterol and a significant decrease in HDL-cholesterol [30]. There are some evidences that the alteration in lipid profile caused by AAS abuse is reversible after some weeks to 3–5 months [5,17,31]. Urhausen *et al.* [7] showed that HDL-cholesterol concentration was normalized one year after the use of AAS be discontinued. Despite these considerations, seems that normalization of the serum lipoproteins levels to be depends strongly on the duration of an AAS course.

In the present study significant increase in hemoglobin, hematocrit, erythrocytes, leukocytes and monocytes were observed in the AAS group, although the values were within the normal range for adult males. Similar findings were found by Urhausen *et al.* [7] in athletes abusing of AAS. The greater number of blood cells in AAS users could be related to the action of androgens on the bone marrow, which increases the number of erythropoietin-responsive cells [7,14,32]. The increase in circulating erythrocytes could increase blood viscosity [14]. Increased hematocrit values are correlated with an increased prothrombotic risk and mortality [33]. The significant alteration in monocytes number may be related to the greater susceptibility of AAS users to the premature development of atherosclerosis [7,8]. The transformation of monocytes in permanently rooted tissue macrophages contributes to foam cell formation and early atherosclerotic plaque formation [7,8,10]. Increased leukocyte count has been associated with an increase in the enzymatic activities for metabolizing androgens [12].

In our study, the AAS users presented higher blood glucose concentration during the post-exercise recovery time. Hyppa [34] demonstrated in AAS-treated horses that the

exercise-induced elevation of glucagon remained increased during the post-exercise recovery time. Since glucagon stimulates hepatic glycogenolysis, their persistence during the postexercise time contributes to the higher glucose concentration observed. On the other hand, previous report has shown diminished glucose tolerance in powerlifters using supraphysiological doses of AAS [35]. This effect may be attributed to an AAS-induced insulin resistance [36,37]. However, the intensity, time of duration and volume of exercise-training seems influence in changes of this variable.

The higher blood lactate concentration after submaximal exercise in AAS users is in accordance with previous observation that AAS users presented a higher exertion score at lower workload [19]. Administration of testosterone induces an increase in the rate of lactate transport from skeletal muscle, associated with increased plasmalemmal density of the monocarboxylate transporter (MCT) 1 and 4 [38]. An increase in MCT 4 protein expression in fast-twitch skeletal muscles has been associated with an increase in glycolytic capacity [39]. Hence, the greater blood lactate production seen in AAS users may be related to serum testosterone level and skeletal muscle type II fiber area [40].

Conclusions

In conclusion, the present findings suggest that young men practicing sports in fitness academies users abusing AAS exhibit proatherogenic and prothrombotic profile, in despite of regular physical activity practice. The higher post-exercise lactate and glucose concentrations in the blood of AAS users suggest premature metabolic alteration. Since these profiles are associated to increased risk of cardiovascular disease, further work is needed to determine potential clinical outcomes associated to AAS abuse.

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