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Original article

Effects of short-term L-arginine supplementation on lipid profile and inflammatory proteins after acute resistance exercise in overweight men

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SUMMARY

Background & aim: Dyslipidemia is involved with in development of cardiovascular diseases and obesity, exercise is recommended as a successful intervention. Dietary L-arginine (L-arg) supplementation may improve in lipid metabolism. However, these combined strategies on lipid profile were not tested yet. This study examines the effects of short term of L-arg supplementation and acute resistance exercise (AREX) on the blood lipid profile and inflammatory proteins in overweight men.
Methods: Seven overweight men, 46 ± 5 yrs, body weight 93.1 ± 12.0 Kg and BMI 31.7 ± 3 kg/m^2, participated in a randomized, double-blind and crossover study, distributed into exercise groups, based on the supplementation (6 g/day of placebo or Arginine for 7 days). Supplementation periods were separated by 7-days of wash-out. The AREX was comprised of eight exercises, with an exercise intensity of 60% 1RM. The glucose, lipid profile (NEFA, triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol) and inflammatory proteins [plasminogen activator inhibitor-1 (PAI-1) and adiponectin] were determined at rest, immediately, after exercise and 1 h after exercise sessions.
Results: Triglycerides, total cholesterol, and adiponectin levels not showed time-dependent changes under the different conditions. LDL cholesterol and NEFA levels decreased after 1 h recovery periods when compared to rest periods only in L-arg supplementation group ($P < 0.05$). PAI-1 was reduced and HDL cholesterol exhibits increases immediately after AREX and 1 h recovery periods when compared with rest periods in both groups ($P < 0.05$).
Conclusion: These results indicate that L-arg supplementation can potentiate the effects of exercise inducing changes in the LDL cholesterol and NEFA levels.

1. Introduction

It is known that physical inactivity is related to excess plasma lipoproteins concentration, which contributes to increased disease risk as: atherosclerosis, hypertension, diabetes, and obesity,[1–3] as well as with many other diseases that are linked to inflammatory markers in the plasma, which includes reduced plasmatic adiponectin, increased

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C-reactive protein (CRP) and increased plasminogen activator inhibitor-1 (PAI-1).[2,4,5]

Exercise (acute or chronic) shown favorably effects on plasma lipid profile.[6] However, other strategies associated or not are recommended to reduced lipid profile, including the use of statins, tea extracts, and some amino acids such as arginine.[7–9]

L-Arginine (L-arg) is a conditionally essential amino acid in human diet that serves as the substrate for nitric oxide synthases (NOS). Boger (2008),[7] showed the ability of dietary L-arg supplementation to improve the functional properties of the cardiovascular system.

Some authors shown that L-arg improves the metabolic profile.[10,11] Although its effects in adipose tissue (improves insulin sensitivity, immune status, hypertension) are well documented,[12–14] the effects of short-term of L-arg supplementation combined with AREX on lipid profile and inflammatory proteins in overweight men remain unclear.

Given the paucity of studies investigating the effects, and combination of L-arg supplementation with AREX on lipid profile, and inflammatory protein. We hypothesized that short-term L-arg supplementation combined with AREX may induce a beneficial effect on lipid profile and inflammatory proteins in overweight men.

2. Methods

2.1. Subjects

Seven overweight, hypertensive men, non-smoking and sedentary with a mean age of 46 ± 5 yrs, body weight 93.1 ± 12.0 Kg and body mass index (BMI) 31.7 ± 3 kg/m^2, participated in this study. At protocol, benefits and risks were explained before written consent was obtained. The study procedures were previously approved by the Ethics Committee of the Universidade Federal de São Paulo – CEP #001/10. Food intake of macronutrients, arginine and energy was made from records during the experimental periods.

2.2. Supplementation

The supplementation was oral administration of L-arg (Sigma®) or placebo (starch) gelatinous capsules (2 g, three times on day) for one week.[15] The study used a 2-supplementation, double blind, randomized and crossover design. Supplementation periods were separated by 7-days washout for change supplementation. The placebo capsules were at the same size, color and flavor as the L-arg capsules.

2.3. Acute resistance exercise session

After medical evaluation, the volunteers underwent three sessions of exercise adaptation to learn the correct technique for the execution of movements. The exercises were conduced at the Centro de Estudos em Psicobiologia e Exercício (CEPE). After the adaptation we performed one maximum repetition (1 MR) test, to determine the percentage of the workload for all exercises. The maximum weight lifted in a single repetition was identified as the 1 MR.

The volunteers performed four sessions of AREX, in three sets of 12 repetitions, as shown in the study design (Fig. 1). The intensity of the exercise session was 60% of 1RM and the method was alternated by segment, beginning with exercises that required a larger muscle group and then moving to the smaller one. The following weight machine (Technogym®, Italy), exercises comprised the AREX: chest press, leg press, handle back, leg extension, deltoids, leg curl, biceps curl, and triceps pulley. The execution speed of 2:2 was used with recovery intervals of 60 s between sets and two minutes between exercises. Before each exercise session, stretching exercises for the major muscle groups were performed.

2.4. Blood sampling and analysis

A baseline blood samples were collected after fasting for 12 h. Blood samples (10 mL) were immediately allocated into two 5-ml vacutainer tubes (Becton Dickinson, BD, Brazil) containing EDTA for plasma separation. The tubes were centrifuged at 2500 g for 12 min at 4 °C, and plasma samples were stored at −20 °C until analysis. Triglycerides, HDL-cholesterol, total cholesterol were assessed trough commercial enzymatic kits (Labtest®, Brazil). LDL-cholesterol was calculated according to Friedewald et al.[16] Plasma glucose concentration was analyzed using the enzymatic colorimetric method (Biotécnica, Brazil). PAI-1 and adiponectin were assessed through commercial kits (R&D systems®, Brazil).

2.5. Statistical analyses

The data distribution was previously checked by Shapiro–Wilk's test and the data are reported as mean ± standard error of the mean. The differences for the blood parameters were evaluated by a 2 × 2 factorial with 2 supplements (placebo or arginine) and two AREX sessions (before and after exercise). The ANOVA with covariance structure and the confidence interval were adjusted by the Bonferroni test. The supplementation and exercise were also evaluated for interaction effects. The analysis was conducted using GraphPad Prism (version 5.0) software, and the significance level was set at $p < 0.05$.

3. Results

In Table 1 are described the baseline characteristics of subjects. It was observed that, fat mass (%), BMI and waist circumference/Hip circumference were bigger than the considering normal ranges to

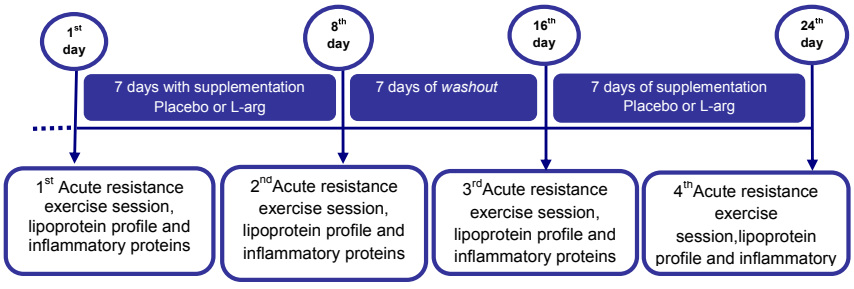

Fig. 1. Study design.

Table 1
Baseline characteristics of volunteers.

Parameters	Mean ±SD ($n = 7$)
Age (years)	46 ± 7
Weight (kg)	93.11 ± 10.43
Height (cm)	171.25 ± 0.06
BMI (kg/cm^2)	31.96 ± 2.33
Systolic blood pressure	127 ± 14.7
Dyastolic blood pressure	78 ± 11.7
Waist circumference/hip circumference	1.01 ± 0.06
Fat mass (%)	30.41 ± 7.07
Lean body mass (kg)	64.46 ± 6.25
Medications	
Angiotensin converting enzyme inhibitor	7

healthy, and characterized this volunteers as overweight and this fact can be correlated to several risk factors.

The volunteers did not show differences between the weeks of supplementations (Table 2). However, the food intake was considered irregular and imbalance, with a high (%) intake of lipids and energy, what may contributed to maintaining overweight in these volunteers and could influence their health.

Table 3 shows the triglycerides (TG), HDL-c, total cholesterol (TC), glucose, and adiponectin levels, before and after supplementation and in the rest, after exercise and 1 h after exercise periods. No significant differences were observed for TG, TC, glucose, and adiponectin over time or between different supplements. HDL-c levels exhibited (tendency, $p < 0.055$) an increased for factor "time" in the after exercise and 1 h after exercise measurements when compared with the rest period in both supplementation conditions.

Figure 2A and B showed that only the combination of L-arg supplementation with AREX induced significant effects in LDL-c and NEFA levels. LDL-c (2.71 ± 0.55 vs 3.27 ± 0.76 mmol/L) and NEFA (264.84 ± 16.25 vs 399.00 ± 56.76 μM) levels were reduced 1 h after exercise when compared with rest period, both statistically significant ($p < 0.05$). After L-arg supplementation also demonstrated significant difference when compared with after placebo supplementation 1 h after exercises ($p < 0.05$).

Figure 3 showed that AREX induced significant effects in PAI-1 levels by reduced levels after exercise and 1 h after exercise when compared with the rest period (5.64 ± 3.06 vs 4.25 ± 0.92 vs 8.90 ± 1.18 ng/mL), after placebo supplementation (4.99 ± 2.45 vs 5.00 ± 1.09 vs 7.24 ± 2.32 ng/mL), before L-arg supplementation (5.58 ± 2.93 vs 5.50 ± 2.76 vs 7.64 ± 4.16 ng/mL), and after L-arg supplementation (5.38 ± 1.88 vs 5.20 ± 1.17 vs 7.76 ± 2.27 ng/mL) all $p < 0.05$.

4. Discussion

Several studies have indicated that in both, animals and humans, L-Arg supplementation may be a novel therapy for the metabolic-related disorders, reducing adiposity and blood pressure while improving insulin sensitivity.[7,12,13]

Lucotti et al.[17] demonstrated that a short period (21 days) of change in lifestyle (a low calorie diet- 1000 kcal/day) and a regular exercise- training program (45 min twice a day for 5 days/week) in

Table 2
Food intake of macronutrients, energy and arginine during 7 days of supplementation with arginine or placebo.

	Arginine supplementation week	Placebo supplementation week
Energy (kcal/kg/day)	40.79 ± 2.70	39.10 ± 2.75
Arginine (g/kg)	0.14 ± 0.01	0.06 ± 0.01
Carbohydrates (g/kg)	4.79 ± 0.43	4.57 ± 0.50
Proteins (g/kg)	1.71 ± 0.14	1.38 ± 0.08
Lipid (g/kg)	1.62 ± 0.16	1.73 ± 0.13

Results are expressed as mean ± SEM. Paired t-test.

Table 3
Lipid profile, glucose, and adiponectin levels at rest, after exercises and 1 h after exercises before and after supplementation with arginine or placebo for 7 days.

	Placebo supplementation		Arginine supplementation	
	Before	After	Before	After
Triglycerides (mmol/L)				
Rest	1.44 ± 0.11	1.58 ± 0.29	1.57 ± 0.23	1.62 ± 0.42
After exercise	1.51 ± 0.26	1.66 ± 0.30	1.74 ± 0.39	1.62 ± 0.42
1 h after exercise	1.45 ± 0.25	1.68 ± 0.35	1.76 ± 0.63	1.63 ± 0.41
Total cholesterol (mmol/L)				
Rest	4.28 ± 0.89	4.49 ± 0.84	4.44 ± 0.53	4.35 ± 0.78
After exercise	4.43 ± 1.06	4.61 ± 1.01	4.54 ± 0.65	4.32 ± 0.55
1 h after exercise	4.37 ± 0.78	5.06 ± 1.50	4.25 ± 0.78	3.92 ± 0.53
HDL-c (mmol/L)				
Rest	0.89 ± 0.13	0.80 ± 0.17	0.80 ± 0.20	0.75 ± 0.11
After exercise[a]	1.00 ± 0.14	0.81 ± 0.19	0.85 ± 0.12	0.90 ± 0.26
1 h after exercise[a]	0.97 ± 0.21	1.00 ± 0.35	0.89 ± 0.21	0.88 ± 0.21
Glucose (mmol/L)				
Rest	5.43 ± 0.90	5.08 ± 0.64	5.15 ± 0.57	5.55 ± 0.43
After exercise	5.67 ± 1.14	5.29 ± 0.51	5.49 ± 0.80	5.92 ± 1.00
1 h after exercise	5.07 ± 0.65	5.58 ± 0.77	5.47 ± 0.69	6.18 ± 1.03
Adiponectin (μg/mL)				
Rest	3.17 ± 1.37	4.08 ± 1.83	3.13 ± 1.77	3.06 ± 1.65
After exercise	3.06 ± 1.46	3.05 ± 1.63	3.46 ± 2.13	3.31 ± 1.21
1 h after exercise	3.02 ± 1.41	2.83 ± 1.75	2.79 ± 1.60	3.25 ± 1.43

Results are expressed as mean ± SEM.
[a] Border line to main effect of time (after exercise and 1 h after exercise vs rest; $p = 0.055$).

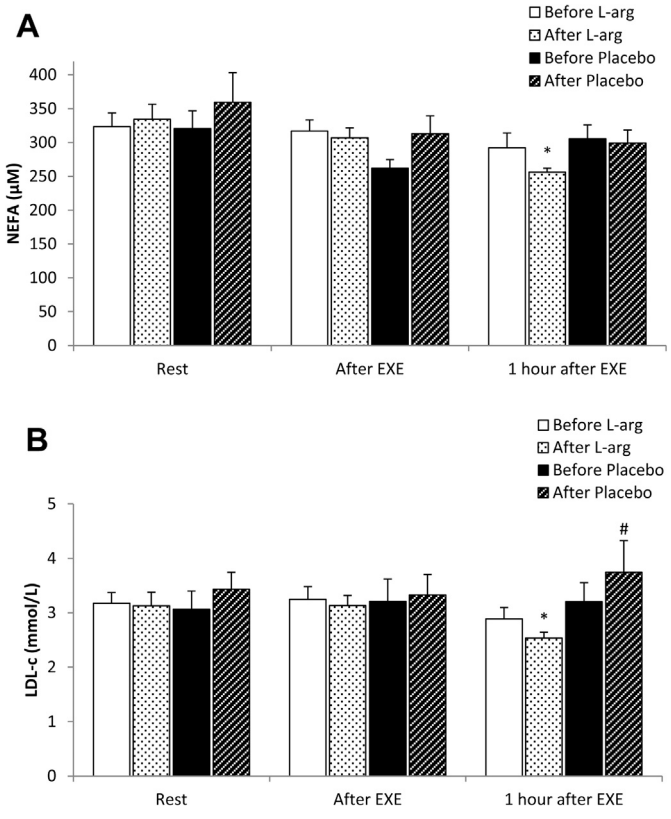

Fig. 2. NEFA and LDL-c levels at rest, after EXE and 1 h after EXE, before and after supplementation with arginine or placebo for 7 days. * = $p < 0.05$ vs rest (after L-arg); # = $p < 0.01$ vs 1 h after exercise (after L-arg). EXE = exercise, L-arg = L-arginine.

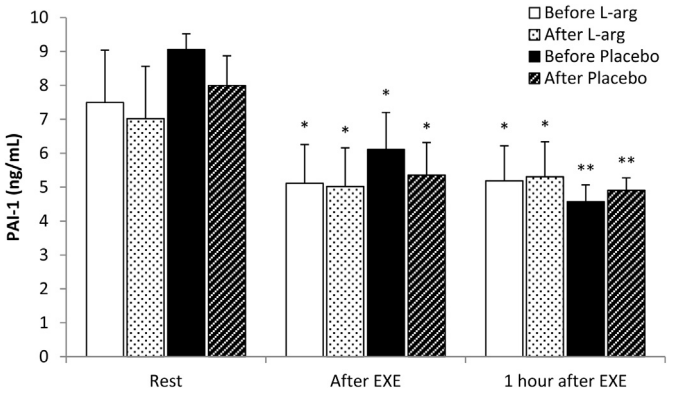

Fig. 3. PA1- 1 levels at rest, after EXE and 1 h after EXE, before and after supplementation with arginine or placebo for 7 days. * = $p < 0.05$ vs respective rest; ** = $p < 0.01$ vs respective rest.

subjects with diet-controlled type-2 diabetes mellitus led to reductions in body weight, fat mass, and circulating levels of glucose and insulin. However, all improvements in the parameters were significantly greater in the L-arg (8.3 g/day) than in the placebo group. Furthermore, in L-arginine group the fat-free mass was preserved. Martina et al.[18] reported that long term supplementation of L-arg (1.2 g/day) combined with N-acetylcysteine (1.2 g/day) for 6 months in hypertensive patients with type 2 diabetes improves endothelial function. Similar results were found by Lucotti et al.[19] in cardiac nondiabetic patients who received L-arg (6.4 g/day) for 6 months after aortocoronary by pass.

Our results indicate that short term L-arg supplementation may potentiate the effects of exercise-induces changes in LDL cholesterol and NEFA in overweight men. For the first time, it was possible to show that a short L-arg supplementation (6 g/day, during 7 days) *per se* can further improve the lipid profile.

The way removes cholesterol from the circulation and distributes it to the peripheral tissues and liver is reverse cholesterol transport pathway.[20] In particular, acute and chronic exercise increase the activity of lecithin-cholesterol aciltransferase (L-CAT), the enzyme responsible for the cholesterol ester transfer to the HDL, which reduces the activity of the plasmatic cholesterol ester transfer protein (CETP), the enzyme responsible in transferring the ester of HDL to other lipoproteins.[21,22] It is possible that the decreased concentrations of LDL-c in the plasma might be attained through the exchange of cholesterol esters from tissues and lipoproteins to the HDL-c.[20]

On the other hand, reduced NEFA levels after L-arg supplementation may result in increased amounts of lipoprotein lipase in skeletal muscle. Magkos,[6] recently described possible methods of VLDL and fatty acid removal from plasma: hydrolysis by lipoprotein lipase (LPL) and possibly also by hepatic lipase, transfer of TG to other lipoproteins (e.g., HDL) via neutral lipid exchange, conversion of VLDL to lipoproteins of higher density, i.g., intermediate-and low-density lipoproteins (IDL and LDL, respectively), and removal of the entire VLDL particle from plasma via interaction with hepatic and/or peripheral receptors.

It's known that regular physical exercise can induce an augmentation of LPL gene expression and activity in the skeletal muscle, resulting in decreased plasma TG and fatty acids content.[23]

In a recent study Lira et al.,[24] reported evidences that corroborates the hypothesis that AREX at a moderate intensity (as well as aerobic exercise) may have anti-atherogenics effects, particularly throughout lipid profile modulation. We demonstrated that AREX may induce changes in the lipid profile in an intensity-specific manner, while also considering the effect of "threshold" on inducing benefits to the lipid profile (low to moderate intensities, at 50% and 75% 1 MR, respectively, seem to be more beneficial to the lipid profile than high intensities of 90% and 110%, 1RM exercise).

The mechanisms activated by L-arg supplementation in organism are less knows. In a recent review, McKnight et al.[12] noted that L-arg can act upon complex mechanisms at the molecular and cellular levels, it can also stimulate mitochondrial biogenesis and brown adipose tissue development, and can regulate gene expression and cellular metabolic pathways. Clemmensen et al.[13] demonstrated that dietary L-arg supplementation has substantial effects on an array of metabolic-associated parameters: it reduced WAT, hyperphagia, improved insulin sensitivity and increased energy expenditure in mice that were fed a low-protein diet.

In animal models, Tan et al.[25] demonstrated that L-arg differentially regulates the expression of fat-metabolic genes in skeletal muscle and white adipose tissue, therefore favoring lipogenesis in muscle but lipolysis in adipose tissue.

It is possible that L-arg can regulate gene expression by removing cholesterol from the circulation via L-CAT and CETP. However, Vega-López et al.,[26] observed that diets with different lysine-to-arginine (Lys:Arg) ratio had no or small effects on cardiovascular risk factors and vascular reactivity. This study was a randomized cross-over design of two 35-day diet phases and included thirty adults (21 females and 9 males, >50 years and with LDL cholesterol > 120 mg/dL). No differences were observed in fasting or postprandial totals; LDL, HDL and apo B concentrations; LCAT or CETP activities. Future studies should address the ability of short and long-term L-arg supplementation to alter gene expression and the activity of the proteins that are involved in reverse cholesterol transport.

Additionally, we observed that HDL levels exhibits (tendency, $p = 0.055$) an increasing after exercise and 1 h after exercise measurements when compared to the rest period in both supplementation conditions, reinforcing role anti-atherogenic of AREX.

We also observed that AREX *per se* promotes lower PAI-1 levels. Jovin et al.[27] showed that plasma LDL-c can induce the release of PAI-1 by endothelial cells into the vessel lumen and can contributes to the release of PAI-1 into the subendothelial space and thus to the process of atherosclerotic plaque remodeling and rupture. The fibrinolytic system is a proteolytic enzyme system with many physiological functions, of which, degradation of fibrin deposits in blood vessels is the best known, and possibly, the most important. Studies have indicated that reduced fibrinolytic capacity, mainly due to elevated plasma levels of PAI-1, may have pathogenetic importance in myocardial infarction, particularly in patients with hypertriglyceridemia.[28]

Nagelkirk et al.,[29] observed that in healthy women, AREX (6 sets of 10 leg extension repetitions at 70% − 1 MR) increased fibrinolytic stimulation; however, there was no change in PAI-1 activity. Further, Baynard et al.[30] examined the effect of different physical activity patterns on fibrinolysis and vasodilatory capacity using a cross-sectional design with endurance-trained, resistance-trained, and untrained men. The authors found that the trained subjects demonstrated anti-atherogenic profile, showing lower PAI-1 levels than the sedentary group. Similar results were found by Lira et al.,[5] who demonstrated that a lifestyle associated with high-intensity and high volume exercise induces changes favorable in the lipid profile and PAI-1 levels, which may be reduce risk for cardiovascular diseases.

In summary, our results indicate that short-term L-arg supplementation combined with resistance exercise induced a reduction in LDL-c and NEFA levels. Additionally, we observed that resistance exercise probably promotes these protective effects by reducing PAI-1 levels. Taken together, short-term L-arg supplementation combined with resistance exercise induces anti-atherogenic effects that can

possibly reduce cardiovascular events. Studies with a long-term supplementation with L-arg, more volunteers and others kind of exercises would be necessary to better clarify this lack in the literature.

Statement of authorship

MAN, EMSH, MTM, ST, SMS, contributed to the study design, protocol, and grant writing. LMO, JAF, EMR, GDP analyzed samples, and contributed to prepare it for publication. MAN, RVS, EMSH, FSL wrote the manuscript and conducted statistical analysis with input and advice from all authors. All read and approved the final manuscript.

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Conflict of interest statement

All the authors declare no competing interests.

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