

**A SINGLE DOSE OF ORAL ATP SUPPLEMENTATION IMPROVES
PERFORMANCE AND PHYSIOLOGICAL RESPONSE DURING LOWER BODY
RESISTANCE EXERCISE IN RECREATIONAL RESISTANCE TRAINED MALES**

Short title: ATP supplementation and performance in resistance trained males.

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1 ABSTRACT

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3 The aim of this study was to investigate the acute effect of ATP supplementation on
4 performance and physiological responses during resistance exercise in recreationally resistance
5 trained males. Eleven men (age= 27.5±5.5 yrs, weight= 83.4±9.8 kg, height= 182±0.04 cm)
6 completed two randomized, double-blind trials: ATP supplement condition (ATP=400mg) or a
7 placebo condition. Thirty minutes after supplement consumption, subjects performed four sets
8 of half-squats until momentary muscular failure at 80% of the 1RM with two minutes of
9 recovery between sets. The total number of repetitions, blood pressure, heart rate, blood lactate,
10 and oxygen consumption were evaluated. The total weight lifted were higher for the ATP
11 condition compared to placebo (Placebo= 3995.7±1137.8, ATP= 4967.4±1497.9 Kg; $p= 0.005$).
12 Heart rate was higher at set-4 for ATP compared to placebo ($p<0.001$) and oxygen consumption
13 during exercise was greater for ATP ($p=0.021$). There were no differences between conditions
14 for lactate and blood pressure. In summary, a single oral dose of ATP supplementation
15 improved lower body resistance training performance and energy expenditure in recreational
16 resistance trained males.

17

18 **Keywords:** ATP supplementation, strength exercise, nutrition.

19

20 INTRODUCTION

21

22 Since the ability to increase lean mass and strength progressively diminishes with training
23 experience (3), many competitive and recreational athletes supplement with nutrients and other
24 compounds with purported ergogenic effects. The use of dietary sport supplements in
25 conjunction with resistance training has been studied to maximize fat loss, muscle hypertrophy
26 and performance (23,14). Adenosine-5'-triphosphate (ATP) is the primary source of energy for
27 muscle cells, and the ability to rapidly resynthesize or maintain intramuscular ATP during

28 intense exercise enhances performance. As such, orally administered ATP is found in several
29 products on the supplement market.

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31 To our knowledge, the first study to evaluate the effects of oral ATP administration was
32 performed by Jordan et al. (18). Subjects consumed a placebo, 150 mg or 225 mg of enterically
33 coated ATP for 14 days. In addition to post testing, an acute test (1 hour post ingestion) was
34 performed on day 1. Oral ATP supplementation did not increase whole blood or plasma ATP
35 concentrations, nor did it improve any metric of performance measured via the anaerobic
36 Wingate test either acutely or sub-chronically. There were no differences between groups sub-
37 chronically for bench press 1 RM, however, the 1 RM of the group ingestion 225g mg ATP was
38 significantly greater during the acute test. The group consuming 225 mg ATP performed more
39 repetitions during 3 sets of bench press to fatigue with 70% of the 1 RM compared to the 150
40 mg ATP and placebo group.

41

42 Utilizing a crossover design with a 1 week washout period, Rathmacher et al. (28) reported
43 that 14 days of 400 mg/day ATP supplementation did not enhance peak torque during 3 sets of
44 50 knee extension contractions, nor average power, total work, or a decrease in work fatigue in
45 active young adults. A small improvement in torque during the final 10 repetitions of the set and
46 a trend for lower fatigue in the third set were found. These results in addition to the
47 improvement in total repetitions reported by Jordan et al. suggest that ATP supplementation
48 may be most ergogenic when the exercise task is fatiguing; however, the ambiguity in findings
49 necessitates a need for further research.

50

51 Several studies have investigated the chronic effects of ATP supplementation on strength
52 and hypertrophic adaptations. Wilson et al. (35) reported that oral supplementation of ATP (400
53 mg/day) combined with resistance training for 12 weeks increased muscle mass and strength in
54 resistance-trained males. Lowery et al. (22) reported a synergistic effect between ATP and beta-
55 hydroxy-beta-methylbutyrate on lean body mass and strength during 12 weeks of resistance

56 training. Although these studies suggest chronic ATP supplementation may enhance
57 hypertrophic adaptations, discrepancies in the methods and inconsistencies in the reporting of
58 the group characteristics (27) call into question the results of the aforementioned studies, and no
59 other studies have evaluated hypertrophic adaptations associated with chronic ATP
60 supplementation.

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62 Because extracellular ATP is tightly regulated at very low concentrations (15), it is unlikely
63 that ATP is absorbed intact in humans (4), which would explain why despite increases in
64 performance have been observed with ATP supplementation, increases in plasma ATP
65 following supplementation have not (Jordan et al.). The ergogenic effects of ATP
66 supplementation may therefore be the result of extracellular ATP carried by red blood cells
67 signaling purinergic receptors, which control blood flow and muscle excitability (7). During
68 exercise extracellular ATP is released from blood erythrocytes (7, 25). When ATP binds the
69 P2Y receptor in endothelial tissue, the synthesis of vasodilator substances occurs (nitric oxide,
70 prostaglandin and endothelial-derived hyperpolarization factors), thereby potentially enhancing
71 the supply of oxygen and nutrients to the active muscles during exercise (13). Although oral
72 ATP supplementation likely does not increase the bioavailability of extracellular ATP, Kichenin
73 et al. (19) demonstrated that chronic ATP administration in rats enhanced ATP uptake and
74 synthesis in the erythrocyte. These findings suggest that greater ATP levels in erythrocyte via
75 ATP supplementation may enhance blood flow and exercise performance in humans.

76 Another physiological mechanism that may explain these ergogenic effects is that
77 extracellular ATP can modulate the contractility of skeletal muscle during exercise via the
78 purinergic receptor P2X4. The binding of extracellular ATP at P2X4 receptor increases calcium
79 intracellular influx (30). During intense exercise, the decrease in rate of intracellular calcium
80 influx contributes to reduction of force generation by skeletal muscle (11). Activation of P2X4
81 by extracellular ATP in muscle cell increases the release of calcium by the sarcoplasmic
82 reticulum (30), enhancing muscle production via greater interactions of actin and myosin
83 filaments (16,21).

84

85 The purpose of this study was to investigate the effect of a single dose of ATP
86 supplementation on lower-body resistance exercise performance and the physiological
87 responses in recreationally resistance trained males. We hypothesize that acute ATP
88 supplementation will attenuate fatigue and result in greater resistance training volume and
89 oxygen consumption.

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91

92 **MATERIALS AND METHODS**

93 **Experimental Approach to the Problem**

94 This study utilized a randomized, double-blind design. Subjects completed 3 experimental
95 trials at the laboratory separated by a minimum of 3 days. All trials were performed at the same
96 time (morning) to ensure chronobiological control and were separated by a week. A schematic
97 illustration of the experimental design can be seen in Figure 1A. The first visit aimed to
98 determine anthropometric measurements and 1RM test for half-squat. On the following two
99 visits, each subject consumed randomly either the placebo or ATP supplement. We used a
100 simple randomization techniques for allocation, which ensured that trial participants had an
101 equal chance of being allocated to a given treatment group (10). After that, the participants
102 completed 4 sets of half-squat until momentary muscular failure with a load corresponding to
103 80% of the 1RM and 2 minutes of rest between sets. The total number of repetitions performed
104 was recorded for each set and was used to analyze performance. Blood lactate and oxygen
105 consumption were analyzed during and after resistance exercise to determine metabolic costs.
106 Heart rate and blood pressure also were collected (**Figure 1**).

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Insert Figure 1

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Subjects

Eleven recreationally resistance trained males with at least 1 year of resistance training experience (experience, 3.4 ± 1.5 yr) at a frequency of 3 days per week and 60 minutes per day were recruited for this study. Written informed consent was obtained from all subjects after they had been informed about the purpose and risks of the study. All participants reported that they had not used any dietary supplements for at least six months prior to the study. Subjects were instructed not to use any other ergogenic substances or supplements during the study. The project was approved by the Ethics Research Group of the University of São Judas, São Paulo-SP, Brazil (Protocol number: 66523717.2.0000.0089) and the research was conducted according to the 2008 Revision of the Declaration of Helsinki.

****Insert table 1****

Procedure**Anthropometric Measurements, Supplementation Protocol and Dietary Intake.**

Height was measured on a fixed stadiometer of the Sanny brand, with an accuracy of 0.1 cm and a length of 2.20 m. Body weight was measured using an electronic scale (Filizola PL 50, Filizola Ltda., Brazil), with a precision of 0.1 kg.

A previous pilot study was performed to match the supplements to taste. Approximately 35 ml of each sample was served in 200 mL glass beakers codified with random two digit numbers (1 or 2), under white light at refrigeration temperature (10 to 15°C). The samples were evaluated regarding color, smell and taste via the nine-point hedonic scale (1 = disliked extremely, 9 = liked extremely) according to Villanueva et al (33).

139 Fifteen subjects were escorted to individual booths and the participants received instructions
140 about the use of the specific scale to be used in that session tested each glass. Participants
141 identified similar color, smell and taste between placebo and ATP. Each participant randomly
142 consumed either the placebo (Clight Juice Kraft Foods Brazil - 200 mL: energy 21 kj, 5 kcal,
143 sodium 4,7 mg) or 400mg of oral ATP supplementation (ProMera Health LLC, Norwell, MA,
144 USA - 200ml: 400mg adenosine-5'-triphosphate disodium). The supplement or placebo was
145 ingested 30 minutes prior to the resistance exercise tests supplied in identical bottles (35).

146

147 During the study all participants were instructed not to use any other supplement or
148 ergogenic substance, as well change their regular diet and exercise behaviors. They were also
149 instructed not to consume caffeine 12 h prior to each experimental test. Food questionnaires
150 were distributed to all participants to record their food and fluid intake for 24 h and pre-exercise
151 meal (breakfast) prior to each trial. Participants were instructed to replicate the first trial's
152 dietary intake for the subsequent trial. All food intakes were analyzed for total kilocalorie and
153 macronutrient intakes ((Software - Dietpro version 5.8) to ensure that dietary intake was similar
154 between experimental trials. Database of Brazilian food composition table (TACO) was utilized
155 to calculate dietary intake.

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157 **Blood pressure and heart rate measurements**

158 Subjects were instructed to remain resting awake in silence for 30 minutes,
159 breathing spontaneously in the supine position before and after aerobic exercise. After
160 the procedures had been explained, an elastic strap was placed at the height of the
161 xiphoid process of the subject and a heart rate receptor on the wrist (Polar Electro,
162 model S810i or RS800, Finland).

163

164 Blood pressure and heart rate (HR) were recorded at baseline, 30 minutes post-
165 ingestion, during exercise (post set-1, 2, 3 and 4), post-10, post-20, post-30, post-40,

166 post-50 and post-60 minutes after exercise. The systolic and diastolic blood pressure
167 were measurement using automatic blood pressure monitor (Omron Healthcare brand,
168 Inc., Intellisense, Model HEM 742 INT, Bannockburn, Illinois, USA).

169

170 **Oxygen Consumption, Energy Expenditure and Blood Lactate**

171 To estimate the energy expenditure of all exercise bouts, the sum of the contribution of
172 the three energy systems (aerobic, anaerobic lactic and alactic) was used. The aerobic
173 metabolism was estimated using the oxygen uptake integral during the exercise, the anaerobic
174 alactic was assessed using the fast phase of excess of oxygen uptake as presented by Bertuzzi et
175 al. (6) and the lactic anaerobic contribution using net blood lactate accumulation as proposed by
176 Di Prampero and Ferretti (9).

177

178 Oxygen uptake was measured continuously for 10 min after the exercise protocols using
179 a breathe-by-breath Quark PFT (COSMED, Rome, Italy) system. The blood samples collected
180 from the ear lobe were utilized to analyze the lactate concentration [La-]. This measurement was
181 obtained at rest, between each set and 3, 5, 30 and 60 minutes after trials. The analyses were
182 performed using the lactate analyzer Yellow Spring 1500 Sport (Yellow Springs, USA). For the
183 anaerobic alactic contribution, the fast component of excess post-exercise oxygen consumption
184 (EPOC) was determined using a modified bi-exponential decay equation. The anaerobic alactic
185 contribution corresponded to the product of bi-exponential fast component amplitude and tau (4,
186 36). The aerobic metabolism was estimated by subtracting rest oxygen consumption from
187 exercise oxygen consumption. To estimate the total energy expenditure and oxygen
188 consumption during each protocol, the energy expenditure were summed and converted to kJ,
189 assuming that 1 L of oxygen consumed was equivalent to 20.9 kJ (12).

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193 **Resistance exercise protocol**

194 Before their first trial, subjects completed two familiarization sessions to become
195 acquainted with the 1 RM test procedures and training equipment. Prior to 1RM testing,
196 subjects completed a warm-up protocol, which consisted 5 minutes of walking and subsequent 1
197 set of 10 repetitions at approximately 50% of the 1RM. The load was increased gradually (10–
198 15%) during the test until the participants were no longer able to perform the entire movement,
199 and 3–5 attempts were allowed as previously described (29).

200

201 Prior to the experimental trials subjects performed a warm-up with walking for 5
202 minutes on a treadmill and a subsequent 1 set of 15 repetitions at 30% of 1RM. After 3 minutes
203 of recovery, each participant completed 4 sets until movement failure at 80% of 1RM with
204 normal speed (1-s eccentric and 1-s concentric) and 2 minutes of rest intervals between sets.
205 Two fitness professionals supervised all testing sessions. For better control of the strength test
206 procedures and resistance exercise protocol, a wooden seat with adjustable heights was placed
207 behind the participant in order to keep the bar displacement and knee angle constant on each
208 repetition.

209

210 **Statistical analysis**

211 The data normality was verified using the Shapiro-Wilk test. The comparison of the total
212 weight lifted under the different conditions was analyzed via a repeated measured *t* test. A 2 x 4
213 repeated measures analysis of variance (RMANOVA) with the Bonferroni adjustment for
214 multiple comparisons was used to compare the maximum number of repetitions performed in
215 each set across conditions and time, respectively. A 2 x 12 RMANOVA was used to compare
216 heart rate and blood pressure across condition and time and 2 x 10, 2 x 5 RMANOVA was used
217 to compare lactate, respectively across condition and time. For all measured variables, the
218 estimated sphericity was verified according to Mauchly's *W* test and the Greenhouse–Geisser
219 correction was used when necessary. Statistical significance was set at $p < 0.05$. The effect size
220 for total repetitions performed and workload was calculated via Cohen's *d* ([treatment mean -

221 placebo mean] / pooled standard deviation) whereby a value of > 0.20 was considered small, >
222 0.50 moderate, and > 0.80 large (8). The data were analyzed using the Statistical Package for
223 Social Sciences 17.0 (SPSS Inc. Chicago. IL.USA).

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225

226 RESULTS

227

228 Table 1 presents the mean and standard deviation values for age, body weight, height,
229 experience, resistance training frequency, body composition and dietary intake.

230 Figure 2 shows the differences in performance for placebo and ATP condition. There was a
231 main effect of time ($F= 29.959, p< 0.001$) and statistically significant differences between
232 condition ($F= 12.208, p= 0.006$) but no interaction was observed ($F= 2.145, p= 0.115$). Figure
233 2A shows that the volume decreased during the sets of squat in both conditions and there were
234 statistically significant differences between conditions for total repetitions (Fig.2B: Placebo=
235 40 ± 11 vs ATP= 49.4 ± 11.5 Kg; $p= 0.006$) and total weight lifted (Fig.2C: Placebo= $3995.7\pm$
236 1137.8 vs ATP= 4967.4 ± 1497.9 Kg; $p= 0.005$). Effect sizes were large for number of
237 repetitions ($d= 0.83$) and ranged from moderate to large in the total weight lifted ($d= 0.73$).

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Insert Figure 2

240

241 Figure 3 presents the differences in heart rate and blood pressure in placebo and ATP
242 condition. For Heart rate (bpm) there was a main effect of time ($F= 251.3, p<0.001$) and
243 significant interaction ($F= 3.120, p=0.001$). The Post-hoc test identified a higher HR for ATP
244 condition at set-4 compared to placebo ($p< 0.001$). For SBP (mmHg) there was a main effect of
245 time ($F= 35.106, p< 0.001$) and significant interaction ($F= 2.073, p= 0.028$), but no difference
246 between conditions ($F= 2.070, p= 0.181$). For DBP (mmHg) there was a main effect of time ($F=$
247 $4.399, p< 0.001$) but no differences between conditions or interaction ($p> 0.05$).

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Insert figure 3

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Figure 4 presents the differences in lactate concentrations in placebo and ATP condition.

251

For lactate, there was a main effect of time ($F= 6.019$, $p< 0.001$), and a tendency for a

252

significant difference between condition ($F= 4.766$, $p= 0.05$) but no interactions were observed

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($F= 0.964$, $p= 0.474$).

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Insert figure 4

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Figure 5 presents the differences in oxygen uptake during exercise, EPOC and total oxygen

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consumption. For relative and absolute oxygen uptake during exercise, there were statistically

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significant differences between conditions ($p<0.005$). For EPOC, there were no differences

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between condition when expressed relative to body weight but a significant difference was

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observed in Kcalories ($p= 0.041$). For total oxygen consumption there was difference between

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conditions in Kcalories ($p= 0.041$).

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Insert figure 5

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DISCUSSION

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To our knowledge, this was the first study to investigate the effects of acute oral ATP

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supplementation on performance and physiological responses during lower-body resistance

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exercise in recreationally trained men. The main findings of the present study were that ATP

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supplementation increased performance and oxygen consumption during lower body resistance

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exercise.

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Our results are in agreement with previous studies that have investigated the ergogenic

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effect of ATP supplementation. Jordan et al. (18) showed that 14 days of 225 mg of ATP

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supplementation was effective to increase total weight lifted and number of repetitions to failure

277 (first set) in the bench press exercise, but they found that a lower dosage (150 mg) did not have
278 benefits on performance. Rathmacher et al. (28) reported that 14 days of 400 mg/day ATP
279 supplementation led to small improvements in torque during the final 10 repetitions of a 50
280 repetition set. Given that ATP supplementation did not improve 1 RM (18) nor peak force (28),
281 it is plausible that the ergogenic effects of ATP supplementation are limited to resistance
282 training activities that are of a high volume and carried out with a high degree of muscular
283 fatigue (i.e.: several sets with many repetitions to failure).

284

285 The possible mechanisms by which ATP supplementation enhances resistance exercise
286 performance may be attributed to the effects of extracellular ATP on muscle excitability.
287 Previous studies demonstrated that muscle fatigue and the reduction in force production induced
288 by high intensity contractions is due impairment of calcium release by the sarcoplasmic
289 reticulum (2, 32, 34). Extracellular ATP can modulate the contractility of skeletal muscle by
290 binding to P2X4 receptor and increasing intracellular calcium influx (30). Therefore, it is
291 possible that ATP supplementation may delay the reduction of calcium release during muscle
292 contractions, maximizing muscle strength production by greater interactions of actin and
293 myosin filaments (16, 21); however, further research is needed to investigate this hypothesis.

294

295 Another possible mechanism whereby ATP supplementation may enhance performance
296 during acute resistance exercise is through the effects of extracellular ATP on vascular tissue.
297 During muscle contractions under hypoxic conditions blood erythrocytes releases ATP which
298 binds to the P2Y receptor in the endothelial tissue. This induces production of endothelium-
299 derived hyperpolarizing factor, prostacyclin, and nitric oxide by endothelial cells, relaxing the
300 smooth muscle of the vasculature (7). We found that ATP supplementation increased oxygen
301 uptake during resistance exercise. It is possible that the vasodilatory effects of ATP may have
302 enhanced oxygen delivery to the working tissues thereby resulting in the improved performance
303 observed in this study. In support of this hypothesis, Jager et al. (17) verified the effects of ATP

304 supplementation on blood flow after resistance exercise in rats and humans and reported higher
305 blood flow following resistance exercise with ATP supplementation.

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307 Previous studies demonstrated that total weight lifted can influence energy expenditure
308 during a resistance training session (1, 24). In this study we found an increased energy
309 expenditure during the ATP condition. This suggests that ATP supplementation may increase
310 aerobic energy expenditure, possibly due to a greater volume of work performed. Some studies
311 have demonstrated that total volume has important implications for muscle hypertrophy and
312 strength gains (20, 26, 31). Our findings demonstrate that acute ATP supplementation increased
313 total weight lifted in recreationally trained males during lower body resistance exercise,
314 however, more research is needed to investigate chronic ATP supplementation and resistance
315 training in populations of different training status on body composition and the
316 immunometabolic response to resistance exercise.

317

318 In conclusion, a single dose of ATP supplementation improved performance, oxygen
319 consumption and energy expenditure during lower body resistance exercise in recreational
320 resistance trained males.

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322 PRACTICAL APPLICATIONS

323

324 This study suggests that resistance-training practitioners can supplement ATP prior to a
325 fatiguing, high volume lower body resistance exercise session to enhance total weight lifted and
326 energy expenditure. Additionally, the dose and form of ATP supplementation (400 mg) was
327 well tolerated in this study.

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331 **CONFLICT OF INTEREST:** The authors declare no conflict of interest.

332

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336

337 **TABLES AND FIGURES CAPTIONS**

338

339 **Figure 1**

340 Experimental Design

341

342 **Table 1:** General characteristics of the sample, dietary intake and macronutrient
343 distribution.

344

345 **Figure 2:** Comparison between placebo and ATP condition on the performance.

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347 **Legend:** 2-A= total weight lifted (Kg); 2-B= maximum number of repetitions in each
348 series; a= main effect of time with Bonferroni's test and p-value < 0.05 compared to set-1. b=
349 main effect of time with Bonferroni's test and p-value < 0.05 compared to set-2.

350

351 **Figure 3:** Comparison between placebo and ATP condition on the heart rate and blood
352 pressure.

353 Legend: HR= heart rate (bpm); SBP= systolic blood pressur (mmHg); DBP= diastolic

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355 **Figure 4:** Comparison between placebo and ATP condition on the lactate concentration.

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358 **Figure 5:** Differences on the oxygen uptake during exercise, excess post-exercise oxygen
359 consumption and total oxygen consumption in placebo and ATP condition.

360 Legend: EPOC= excess post-exercise oxygen consumption.

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492 accumulated oxygen deficit. *Scandinavian journal of medicine & science in sports*, 21:222-230,
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494 **Table 1.** General characteristics of the sample, dietary intake
 495 and macronutrient distribution.

Age (y)	27.5±5.5
Height (cm)	182.0±0.04
Weight (kg)	83.5 ±9.8
Squat 1 RM (kg)	127.8±19.7
Dietary Intake 24 hours	
Diet CHO (g)	211,3± 55.8
Diet PRO (g)	149,7±81.1
Diet FAT (g)	54,13±21.7
Total Intake (kcal)	1931±562.1
Dietary Intake Pre-training	
CHO (g)	44,21±18.1
PRO (g)	20,69±9.1
FAT (g)	12,54±6.6
Total Intake (kcal)	372,4±109.8

496 CHO= carbohydrate (g); PRO= protein (g); FAT= lipids (g);

497 1RM= one maximum repetition.

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