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Effects of an antioxidants cocktail on glucose metabolism at rest, during exercise, and during a glucose load in healthy young subjects

Efecto de un cóctel de antioxidantes sobre el metabolismo de la glucosa en reposo, durante el ejercicio y durante una carga de glucosa en sujetos jóvenes sanos

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ABSTRACT

Background: Reactive oxygen species (ROS) regulate glucose metabolism (GM) in skeletal muscle by improving the translocation of GLUT4. Antioxidant supplementation could block this physiological effect, altering glucose signaling during exercise. However, there is limited evidence in humans on whether antioxidant intake affects GM. Therefore, we aimed to determine the effect of an antioxidant cocktail (AOC) on GM at rest and during metabolic challenges. Methods: Ten healthy male subjects received AOC supplementation (1000 mg of Vitamin C, 600 IU of Vitamin E, and 600 mg of α-lipoic acid) or placebo (2.000 mg of talc) before two trials conducted 7 days apart. Trial 1: AOC 120 and 90 minutes before an endurance exercise (EEX) bout at 60 % of maximal oxygen uptake (VO_{2max}); Trial 2: AOC 120 and 90 minutes before an oral glucose tolerance test (OGTT; 75 g glucose). Measurements of gas exchange and capillary blood samples were collected every 15 minutes during both trials. Results: AOC supplementation increased resting glucose levels ($p<0.05$). During Trial 1 (EEX), the AOC increased carbohydrate oxidation (CHOox) ($p= 0.03$), without effect in glucose blood levels. During Trial 2 (OGTT), the AOC supplementation had no significant effect on GM parameters. Conclusion: Acute supplementation with AOC increased resting glucose levels and CHOox during EEX in healthy subjects, with no effect on GM during the OGTT.

Keywords: α-lipoic acid; Glucose metabolism; Substrate oxidation; Vitamin C, Vitamin E.

RESUMEN

Antecedentes: Las especies reactivas de oxígeno (ROS) regulan el metabolismo de la glucosa (GM) en el músculo esquelético al mejorar la translocación de GLUT4. La suplementación con antioxidantes podría bloquear este efecto fisiológico, alterando la señalización de la glucosa durante el ejercicio. Sin embargo, existe evidencia limitada en humanos sobre si la ingesta de antioxidantes afecta el GM. Por lo tanto, nuestro objetivo fue determinar el efecto de un cóctel de antioxidantes (AOC) en el GM en reposo y durante desafíos metabólicos. Métodos: Sujetos sanos (sexo masculino; n= 10) recibieron suplementos de AOC (1.000 mg de vitamina C, 600 UI de vitamina E y 600 mg de ácido α-lipoico) o placebo (2.000 mg de talco) previo a dos pruebas realizadas con 7 días de diferencia. Prueba 1: AOC 120 y 90 minutos antes de una serie de ejercicio de resistencia (EEX) al 60% del consumo máximo de oxígeno (VO_{2max}); prueba 2: AOC 120 y 90 minutos antes de una prueba de tolerancia oral a la glucosa (OGTT; 75 g de glucosa). Se obtuvieron datos de intercambio de gaseoso y muestras de sangre capilar cada 15 minutos durante ambas pruebas. Resultados: la suplementación con AOC aumentó los niveles de glucosa en reposo ($p<0,05$). Durante la prueba 1 (EEX), el AOC aumentó la oxidación de carbohidratos (CHOox) ($p= 0,03$), sin efecto en los niveles de glucosa en sangre. Durante la prueba 2 (OGTT), la suplementación con AOC no tuvo un efecto significativo en los parámetros de GM. Conclusión: Una suplementación aguda con AOC aumentó los niveles de glucosa en reposo y la CHO_{ox} durante EEX en sujetos sanos, sin efecto sobre el GM durante la OGTT.

Palabras clave: Ácido α-lipoico; Metabolismo de la glucosa; Oxidación de sustrato; Vitamina C; Vitamina E.

INTRODUCTION

Antioxidants are widely consumed for promoting health and well-being, showing potential benefits in glycemic control[1], oxidative stress[2], and muscle recovery[3], among others. For instance, consuming antioxidant-rich food or beverages shortly before or during exercise can yield advantageous outcomes, including a delay of fatigue and a shortened recovery period[4]. Thus, the market for antioxidant supplements is continuously growing[5]. These supplements are highly concentrated, and their intake often does not require monitoring by a specialist[6]. Commonly used antioxidant supplements include vitamins C, E, and α-lipoic acid[7,8].

It is well-established that the body's oxidative state is regulated through hormesis. High reactive oxygen species (ROS) levels can lead to deleterious effects (i.e., oxidative distress)[9], whereas moderate ROS levels activate redox signalling pathways necessary for physiological adjustments during metabolic challenges (i.e., oxidative eustress)[10,11,12]. Exercise and high glucose intake are metabolic challenges that induce physiological adjustments to maintain glycemic homeostasis, exhibiting an increment in ROS production due to muscle contraction caused by exercise and glucose metabolism (GM)[13,14]. Contreras-Ferrat et al. (2014) reported that insulin increased cytoplasmic ROS production (i.e., H_2O_2) in skeletal muscle cells (L6-GLUT4myc myotubes). H_2O_2 (0.01–0.1 mM) induced higher translocation of the glucose transporter type 4 (GLUT4) and glucose uptake in the L6-GLUT4myc myotubes. On the other hand, H_2O_2 in higher concentrations (1.0 mM) inhibited GLUT4 translocation[10].

However, there is no consensus about the impact of antioxidant supplementation during metabolic challenges. A meta-analysis conducted by Ashor W. et al. (2017) concluded that acute Vitamin C supplementation positively impacted glycemic control in individuals with diabetes. However, the effects on glycemic control in healthy subjects were inconclusive[1]. The redox response in healthy subjects has exhibited substantial variability when challenged with exercise or high glucose intake[15]. In another meta-analysis regarding supplementation with vitamins C and E (4 – 24 weeks) on exercise adaptation in healthy subjects, the clinical trials discussed showed no effect on VO_{max}, endurance performance, and muscle strength[16].

There is contradictory evidence regarding the consumption of antioxidant supplements on performance and training adaptations in healthy non-active subjects[17], and whether these effects differ at rest or during metabolic challenges is also a pending issue. Therefore, the present study aims to determine the effects of an acute supplementation with an AOC (Vitamin C, E, and α-lipoic acid) on GM at rest and during metabolic challenges, endurance exercise (EEX), and OGTT in healthy subjects.

Methods and materials

2.1 Participants

Ten healthy male volunteers (25 ± 4 years old; body mass index (BMI), 25.5 ± 3.1 kg/m^2 and maximal oxygen uptake (VO_{2max}), 50.6 ± 8.12 mL•kg^{-1}•min^{-1}) participated in this study. Inclusion criteria were having a BMI between 18.5-29.9 kg/m^2, being between 19 and 33 years old, living in the Metropolitan Region (Chile), not performing more than 120 minutes per week of moderate physical activity or 75 minutes per week of vigorous physical activity, and not having consumed antioxidant or multi-vitamin supplements for at least 12 months before the trials. Exclusion criteria were having a history of cardiovascular, respiratory, and thyroid diseases, presenting musculoskeletal problems, and being on pharmacological therapy of any kind. Participants were instructed not to perform physical activity 56 hours prior to the intervention. All the subjects signed the written informed consent before participating. The study was approved by the Institutional Ethic Committee of Finis Terrae University N°21/2017, which adheres to the Declaration of Helsinki.

2.2 Experimental design

The trials were conducted using a double-blind, placebo-controlled, randomized crossover design. Participants were instructed to visit the laboratory on five separate occasions after an 8-hour fasting period. During the initial visit, baseline values of homeostasis model assessment for insulin resistance (HOMA-IR; calculated as fasting glucose multiplied by fasting insulin and divided by 405) were measured, and an incremental exercise test was performed to determine VO_{2max}. Subsequently, participants were requested to return to the laboratory for four additional visits. Two of these visits involved performing an EEX session while consuming either a placebo or an AOC as part of the EEX study. The other two sessions consisted of participants undergoing an OGTT with prior administration of either a placebo or AOC. Each session was separated by a one-week washout period, and the order of the visits was randomized for each subject. Measurements of energy expenditure, respiratory quotient (RQ), carbohydrate oxidation (CHO_{ox}), plasma glucose, lactate, relative oxygen consumption (VO_2), and relative carbon dioxide production (VCO_2) were recorded at rest (0 minutes) and at 15-minute intervals during each trial for a total duration of 60 minutes.

2.3 Maximal Oxygen Uptake test

VO_{2max} was determined using a breath-by-breath pulmonary gas exchange system (Ergocard, Medisoft, Belgium) during an incremental treadmill test. To ensure accurate measurements, the gas analyzer was calibrated using gases of known concentrations (VO_2= 16.0% and VCO_2= 4.0%), while the airflow was calibrated using a 3-liter syringe (Hans Rudolph, Kansas, MO, USA). The test commenced at a speed of 6 km/h and included a slope of 1.5% inclination. Speed increments of 1 km/h were implemented every 120 seconds. VO_{2max} was considered achieved when at least two of the following criteria were met: 1) a plateau in VO_2 despite an increase in workload; 2) a respiratory exchange ratio (RER)≥1.2; and 3) reaching the maximal heart rate expected for the participant's age (calculated as 220 bpm minus the age).

2.4 Antioxidant cocktail supplementation. The AOC was administered in two divided doses, taken at 120 and 90 minutes prior to the trials (EEX or OGTT). The composition of the AOC capsule was based on the protocol used by Donato et al. (2010)[18]. The first dose comprised 500 mg of Vitamin C, 200 IU of Vitamin E, and 300 mg of α-lipoic acid, while the second dose consisted of 500 mg of Vitamin C, 400 IU of Vitamin E, and 300 mg of α-lipoic acid. Placebo capsules containing weight-matched talc were consumed within the same time frame.

2.5 Endurance exercise

EEX was conducted on a treadmill (HP/Cosmos pulsar 3P, Germany) for 60 min at 60% of the participant's VO_{2max}, after an 8-hour fasting period and 90 min after AOC supplementation. Drinking water was allowed during the EEX trial. Heart rate, respiratory rate, VO_2, and VCO_2 were monitored at consistent time intervals throughout the EEX session. Also, the perceived effort was assessed using the Borg Rating of Perceived Exertion scale[19].

2.6 Oral glucose tolerance test and blood glucose and lactate levels

The OGTT was conducted 90 min after administering the second dose of AOC. Participants were instructed to lie supine on a gurney for 20 minutes at 25 °C. Subsequently, they were asked to consume 200 ml of a glucose solution containing 75 g of glucose. Blood lactate and glucose levels were measured using capillary samples obtained through a finger prick at 0, 15, 30, 45, and 60 min after consuming the glucose solution. The subjects were instructed to maintain a resting position until the end of the trial (60′ post glucose solution intake). Samples were immediately analyzed for whole blood lactate concentration (mmol/l) using an enzymatic lactate analyzer (Lactate Pro 2™ Arkray, KDK, Japan). Blood glucose levels (mg/dl) were measured using a blood glucose monitor (Freestyle Optium Neo, Abbott, Chile).

2.7 Gas exchange measurements, whole-body substrate oxidation, and energy expenditure calculation rates

Gas exchange was assessed by a breath-by-breath pulmonary gas exchange system (Ergocard, Medisoft, Belgium). VO_2 and VCO_2 values were determined by calculating the average of the final minute for each time point (0, 15, 30, 45, and 60) during each trial. Whole-body CHO_{ox} and energy expenditure were estimated based on the VO_2 and VCO_2 data, utilizing the equations provided by Frayn 1983[20].

2.8 Statistical analyses

The normality of the data was assessed using the Shapiro-Wilk test. Resting characteristics between trials were compared using Student's t-test. A two-way repeated measure analysis of variance (ANOVA) was employed to compare variables over time and between trials. For multiple comparisons, the Bonferroni post hoc comparison method was used. The significance level was set at p<0.05. All statistical analyses were performed using GraphPad Prism software version 7.0.

RESULTS

3.1 Baseline characteristics and glucose metabolism parameters at rest

Baseline general and fitness characteristics are presented (Table 1). Participants were 25.3±4.2 years old with a BMI of 25.5±3.1 kg/m^2. Fasting glucose was normal

(85.3±8.1 mg/dl), concordant with a normal HOMA-IR of 1.3±0.4. Moreover, the subjects exhibited a VO_{2max} of 50.6±8.1 $mL \cdot kg^{-1} \cdot min^{-1}$. GM parameters at rest (Table 2) show that overall fasting glucose was higher after AOC compared to placebo in both trials ($p = 0.02$ and $p = 0.006$ for EEX and OGTT trials, respectively). No significant differences were observed between AOC versus placebo on lactate and RQ in both trials.

3.2 Acute administration of an antioxidant cocktail increased carbohydrate oxidation during the endurance exercise trial

AOC supplementation or placebo effect in GM and energy expenditure during the EEX trial is presented in Figure 1. There were no differences in plasma glucose (Figure 1A), plasma lactate (Figure 1B), energy expenditure (Figure 1C), and RQ (Figure 1E) when time x group interaction was considered. However, after consuming the AOC, a higher CHO_{ox} was observed at 15 min of performing the EEX (Figure 1E) compared to placebo (time x group interaction, $p = 0.03$). The increment in CHO_{ox} induced by an AOC supplementation was not accompanied by changes in respiratory rate, heart rate, or perception of effort during EEX comparing AOC versus placebo (Figure 2).

3.3 Acute administration of an antioxidant cocktail exhibited a lower plasma glucose tendency, with no statistical differences during the oral glucose tolerance test trial

No interaction between time and group effect was observed between the AOC and placebo intervention for plasma lactate (Figure 3A), CHO_{ox} (Figure 3C), or RQ (Figure 3D) over time during the OGTT. However, a tendency to lower plasma glucose for the AOC compared to placebo was observed considering the group x time interaction at 30 min ($p = 0.05$) and 45 min ($p = 0.06$), with no statistical differences (Figure 3A).

Table 1. Baseline general and fitness characteristics of participants.

Characteristic	n= 10
Age (y)	25.3 ± 4.2
Weight (kg)	75.2 ± 10.1
BMI (weight/height^2)	25.5 ± 3.1
Fasting glucose (mg/dl)	85.3 ± 8.1
Fasting insulin (mg/dl)	5.9 ± 1.8
HOMA-IR	1.3 ± 0.4
VO_{2max} (ml/kg/min)	50.6 ± 8.1

BMI, body mass index; HOMA-IR, homeostasis assessment model for insulin resistance; VO_{2max}, maximal oxygen uptake. Data are presented as mean ± SEM.

Table 2. Glucose metabolism parameters at rest.

	EEX study			OGTT study		
	AOC	Placebo	p-value	AOC	Placebo	p-value
Fasting glucose (mg/dl)	96±7.3	89±6.7	0.02	93±5.4	87±6.1	0.006
Fasting Lactate (mmol/l)	1.7±1.3	1.9±1.2	0.22	1.4±1.2	1.5±1.4	0.41
RQ	0.89±0.11	0.90±0.15	0.90	0.87±0.06	0.89±0.11	0.64

GM, glucose metabolism; EEX, endurance exercise; OGTT, oral glucose tolerance test; AOC, antioxidant cocktail; RQ, respiratory quotient. Data are presented as mean ± SEM. Statistical test T-Student, $p<0.05$ AOC versus placebo.

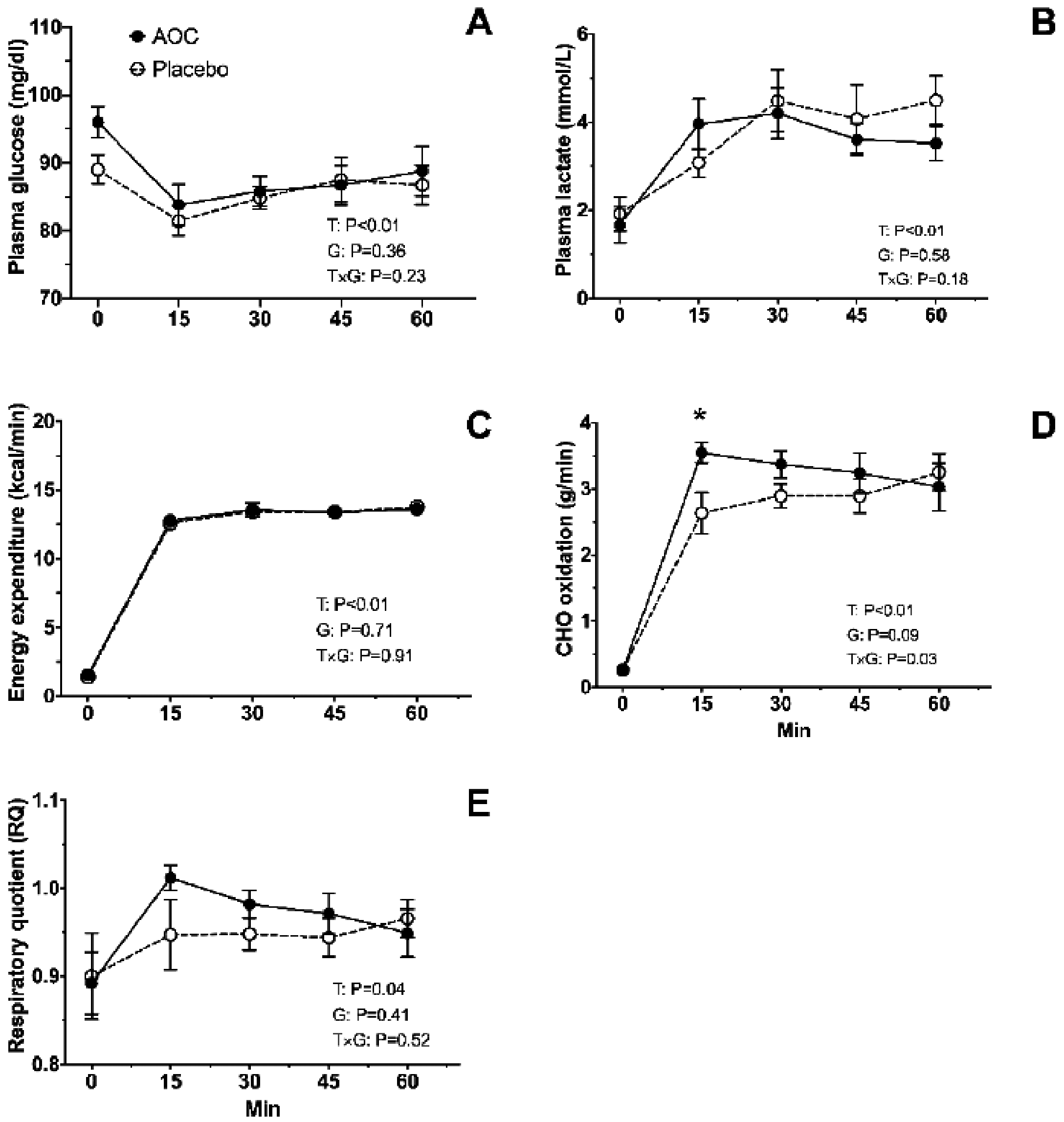

Figure 1: AOC supplementation versus placebo in GM parameters and energy expenditure during an EEX trial. A. Plasma glucose during EEX trial (mg/dl); B. Plasma lactate during EEX trial (mmol/l); C. Energy expenditure during EEX trial (kcal/min); D. CHO_{ox} during EEX trial (g/min); E. RQ during EEX trial. AOC, antioxidant cocktail; GM, glucose metabolism; EEX, endurance exercise; RQ, respiratory quotient; CHO_{ox}, carbohydrate oxidation; T, time; G, group. Data are presented as mean ± SEM test two-way ANOVA. Post-hoc Bonferroni test was conducted when TxG $p<0.05$, symbolized by *.

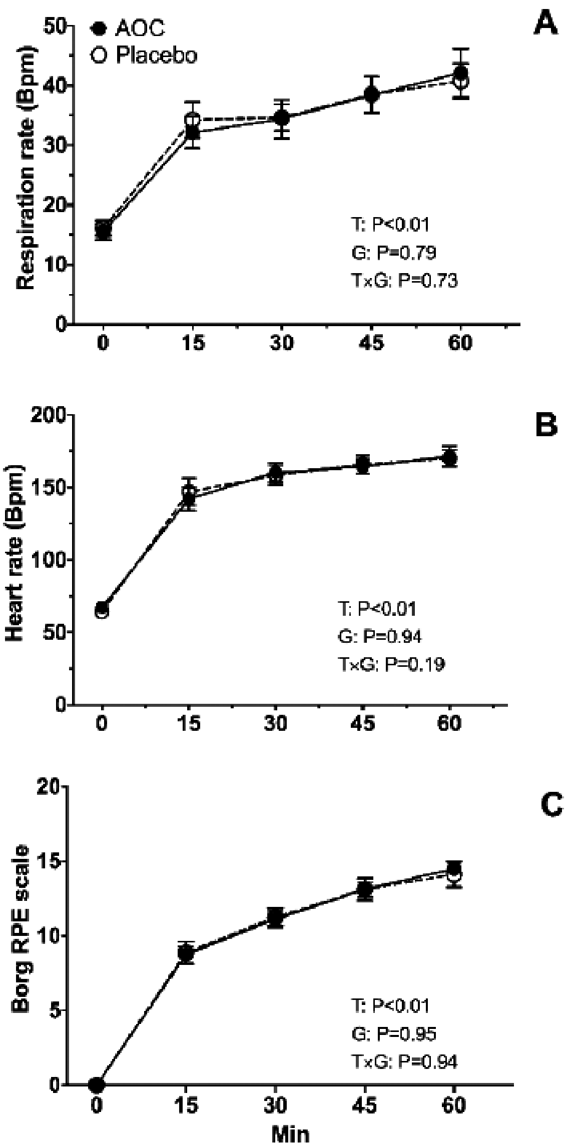

Figure 2: AOC supplementation versus placebo in respiratory rate, heart rate, or perception of effort during an EEX trial. A. Respiratory rate during EEX trial (Bpm); B. Heart rate during EEX trial (Bpm); C. Perception of effort during EEX trial (Borg RPE scale). AOC, antioxidant cocktail; EEX, endurance exercise; RPE, Rating of Perceived Exertion; T, time; G, group. Data are presented as mean ± SEM test two-way ANOVA. Post-hoc Bonferroni test was conducted when TxG $p<0.05$, symbolized by *.

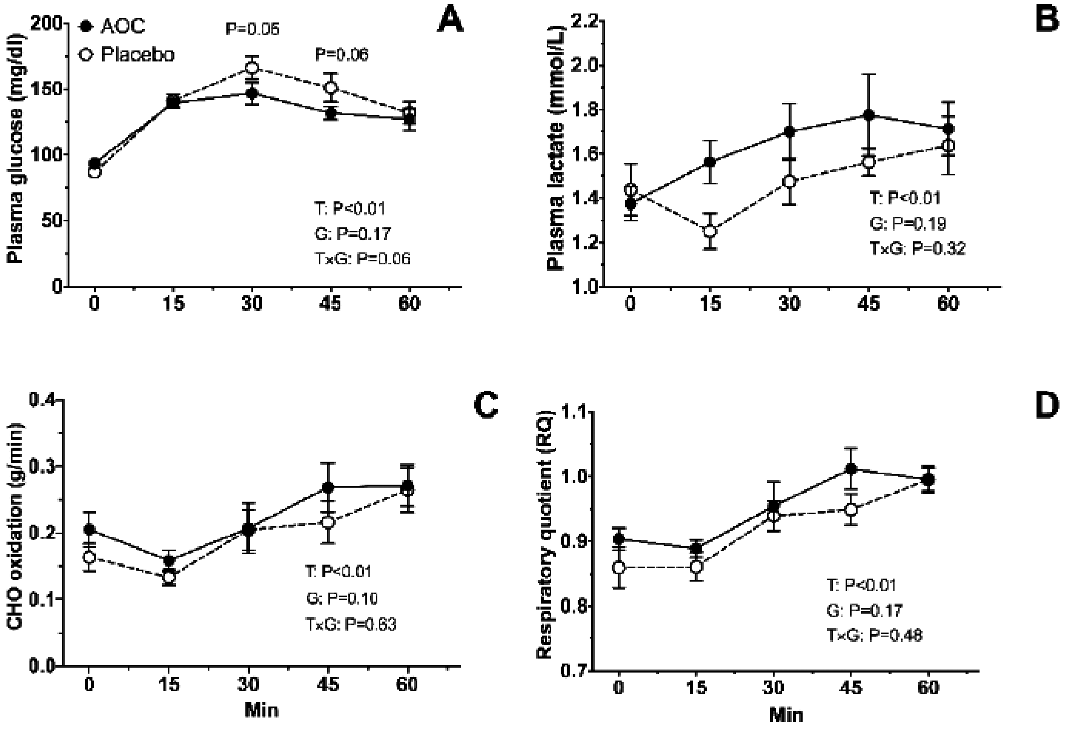

Figure 3. AOC supplementation versus placebo in GM parameters during an OGTT trial. A. Plasma glucose during OGTT trial (mg/dl); B. Plasma lactate during OGTT trial (mmol/l); C. CHO_{ox} during OGTT trial (g/min); D. RQ during OGTT trial. AOC, antioxidant cocktail; GM, glucose metabolism; OGTT, oral glucose tolerance test; RQ, respiratory quotient; CHO_{ox}, carbohydrate oxidation; T, time; G, group. Data are presented as mean ± SEM test two-way ANOVA. Post-hoc Bonferroni test was conducted when TxG p<0.05.

DISCUSSION

This study evaluated the effects of an acute supplementation with an AOC (Vitamin C, E, and α-lipoic acid) on GM at rest and during EEX and OGTT in 10 healthy subjects. No adverse reactions or symptoms were reported following the administration of the supplements.

The results revealed that AOC supplementation led to a 9% increase in resting glucose levels compared to the placebo trial. This could be attributed to alterations in insulin secretion or insulin resistance in peripheral tissues. Previous *in vitro* studies have shown that glucose-induced insulin secretion in INS-1 cells (832/13) is ROS-dependent[11]. Furthermore, glucose uptake in skeletal muscle has been shown to be dependent on insulin-stimulated ROS generation due to NADPH oxidase activation[21]. Considering that antioxidant supplementation has been found to diminish endogenous ROS production[22], it could be suggested that acute intake of an AOC might decrease insulin secretion and glucose uptake in skeletal muscle. In the current study, elevated resting glycemia levels were observed in healthy subjects when an AOC was taken. It is widely recognized that alterations in glycemic control are associated with increased mortality risk[23]. Consequently, the consumption of high acute doses of antioxidants by individuals with insulin resistance may not confer beneficial effects. Nonetheless, this remains an unresolved issue. In a study conducted by Damiot et al., (2019), the impact of a nutrient cocktail containing high levels of antioxidants (vitamin E, polyphenols, and selenium), as well as omega-3 fatty acids, was evaluated in healthy men (n= 20) with metabolic disturbances induced by fructose overfeeding for 20 days. The cocktail did not exhibit any effect on insulin sensitivity but exhibited a preventive effect on alterations in lipid metabolism[24]. Consequently, there is currently insufficient evidence to provide definitive recommendations.

During exercise, it is well known that skeletal muscle contractions generate ROS, which regulate glucose transport capacity[25]. Therefore, it could be speculated that ROS production in skeletal muscle during exercise allows proper glucose uptake and CHO_{ox}. Contrary to expected, our results indicate elevated levels of CHOox at the beginning of the EEX trial (15') when the AOC was taken compared to the placebo. This difference could be explained by the higher resting glucose levels observed before the EEX trial when AOC was taken. Also, trial time could be an important factor to consider. AOC intake may lead to reduced CHO_{ox} compared to placebo following prolonged exercise (i.e., >60 min). During exercise, after glycogen stores are depleted and more extracellular glucose is required[26], ROS signaling stimulates GLUT4 favoring glucose uptake[25]. Thus, high antioxidant doses could impair this physiological adaptation induced by ROS. Other studies combining high doses of Vitamins C and E for extended periods have shown no effect of antioxidant supplementation on physiological exercise adaptations. However, no results regarding GM have been presented[16].

Regarding the OGTT study, AOC supplementation resulted in a slight decrease in plasma glucose levels, although the difference was not statistically significant. Furthermore, no significant differences in CHO_{ox} were observed. Similar findings were reported in individuals with abdominal obesity following acute consumption of 10 g of a high-antioxidant grape/pomegranate pomace nutraceutical (providing 1.8 g polyphenols). The authors noted a trend toward improved insulin sensitivity, although the differences were not statistically significant[27].

Our findings indicate that the acute consumption of an AOC can influence GM at rest and during EEX. Considering that moderate levels of ROS may play an important role in GM and glycemic control, the use of high doses of antioxidants through supplementation could potentially hinder the health-promoting effects of exercise in humans, such as improvements in insulin sensitivity[28]. It is important to note that the doses utilized *in vitro* or in humans consuming AOC are considered mega doses and cannot be directly compared to the antioxidant concentrations found naturally in fruits and vegetables[29]. Moreover, diets rich in fruits and vegetables have consistently demonstrated a significant reduction in cardiovascular risk[30].

This study has limitations. First, there was no control over the participants' diets, and their intake of dietary antioxidants was not assessed. Subjects were advised to adhere to their usual eating habits. Furthermore, the physical activity assessment among the subjects was quite broad, as no comprehensive physical activity survey was administered. This study offers insights into the impact of an AOC on GM during metabolic challenges. Nevertheless, further investigations involving a larger number of participants are essential. Assessing insulin levels, ROS levels, or other oxidative stress markers will be important for a better understanding AOC effect on GM. These future studies should rigorously control for dietary factors and physical activity levels while considering both male and female participants.

CONCLUSION

The acute supplementation of an AOC (Vitamin C, E, and α-lipoic acid) led to elevated resting glucose levels and an increased CHO_{ox} response at the beginning of the EEX metabolic challenge while showing no significant impact during the OGTT challenge in healthy individuals. As a result, acutely administering high doses of antioxidants may have a detrimental effect on basal GM. However, this impairment was not observed during the EEX challenge. While this study was conducted with healthy participants, healthcare professionals should carefully evaluate the need for antioxidant supplementation, especially when dealing with GM irregularities. Further research is required to evaluate the influence of antioxidant supplementation on GM in healthy individuals and those with GM abnormalities.

Authors contribution. *Conceptualization: M. CS.; methodology: M. CS. and H. ZB.; investigation: I.R.; formal analysis: I.R. and E.PE.; writing original draft: I.R. and M. CS.; visualization and writing review and editing: F. E. and M. CS. All authors have read and agreed to this version of the manuscript.*

Conflict of interest. *There are no conflicts to declare.*

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