

Effects of Supplemental Citrulline-Malate Ingestion on Blood Lactate, Cardiovascular Dynamics, and Resistance Exercise Performance in Trained Males

Benjamin Wax, PhD¹, Andreas N. Kavazis², & William Lockett³

¹Kinesiology, Mississippi State University, Meridian, Mississippi, USA, ²Kinesiology, Auburn University, Auburn, Alabama, USA, ³Mississippi State University, Meridian, Mississippi, USA

ABSTRACT. Citrulline-malate (CM) has been proposed to provide an ergogenic effect during resistance exercise; however, there is a paucity of research investigating these claims. Therefore, we investigated the impact that CM supplementation would have on repeated bouts of resistance exercise. Fourteen resistance-trained males participated in a randomized, counterbalanced, double-blind study. Subjects were randomly assigned to placebo (PL) or CM (8 g) and performed three sets each of chin-ups, reverse chin-ups, and push-ups to failure. One week later, subjects ingested the other supplement and performed the same protocol. Blood lactate (BLa), heart rate (HR), and blood pressure (BP) were measured preexercise, with BLa measured a second time immediately following the last set, while HR and BP were measured 5 and 10 min postexercise. Citrulline-malate ingestion significantly increased the amount of repetitions performed for each exercise (chin-ups: PL = 28.4 ± 7.1, CM = 32.2 ± 5.6, $p = .003$; reverse chin-ups: PL = 26.6 ± 5.6, CM = 32.1 ± 7.1, $p = .017$; push-ups: PL = 89.1 ± 37.4, CM = 97.7 ± 36.1, $p < .001$). Blood lactate data indicated a time effect ($p < .001$), but no treatment differences ($p = .935$). Systolic BP data did not show differences for time ($p = .078$) or treatment ($p = .119$). Diastolic BP data did not show differences for time ($p = .069$), but indicated treatment differences ($p = .014$) for subjects ingesting CM. Collectively, these findings suggests that CM increased upper-body resistance performance in trained college-age males.

KEYWORDS. ergogenic aid, nutrition, strength training, supplement

INTRODUCTION

Athletes and fitness enthusiasts are continuously seeking mechanical and nutritional aids that may provide them with the competitive edge during training and for competitive purposes. Exogenous substances that provide this enhanced performance are commonly alluded to as ergogenics (Williams, 1999), while those

Address correspondence to: Benjamin Wax, PhD, Kinesiology, Mississippi State University, 1000 Highway 19 N, Meridian, MS 39307, USA (E-mail: bw244@msstate.edu).

impairing performance are called ergolytics (Eichner, 1993). Recently, nitric oxide-related supplements have garnered much attention for their proposed ergogenic properties (Alvares, Meirelles, Bhambhani, Paschoalin, & Gomes, 2011; Bendahan et al., 2002; Bescos, Sureda, Tur, & Pons, 2012; Elam, Hardin, Sutton, & Hagen, 1989; Fahs, Heffernan, & Fernhall, 2009; Fricke, Baecker, Heer, Tutlewski, & Schoenau, 2008). In particular, an over-the-counter supplement called citrulline-malate has been reported to augment energy production (Bendahan et al., 2002), increase blood flow to skeletal muscle, which may contribute to increased performance during repeated bouts of high-intensity resistance exercise (Perez-Guisado & Jakeman, 2010).

Citrulline-malate, sold as a pharmaceutical drug in Spain (brand name Stimol), was originally developed to improve the muscle performance of patients suffering from asthenia and to mitigate recovery time following physical activity for individuals suffering from acute diseases (Creff, 1982). A double-blind study reported that citrulline-malate has an antiasthenic effect on muscle fatigue (Creff, 1982) in disease patients, which may have increased its appeal to athletes seeking to increase athletic performance and decrease recovery times between bouts of intense exercise. Theoretically, this resistance to fatigue may be attributed to augmenting nitric oxide synthesis via citrulline (Gibala, Young, & Taegtmeier, 2000; Goubel, Vanhoutte, Allaf, Verleye, & Gillardin, 1997), which may allow for improved blood flow (Barbul, 1986). This elevation in blood flow could tentatively increase nutrient delivery and/or waste-product clearance (Little, Forbes, Candow, Cornish, & Chilibeck, 2008; Wilcock, Cronin, & Hing, 2006) such as plasma lactate and ammonium via the urea cycle, thereby improving muscle function (Briand, Blehaut, Calvayrac, & Laval-Martin, 1992).

Specifically, L-citrulline is a nonessential amino acid produced endogenously via two key metabolic processes: 1) it is synthesized in the intestinal tract from the amino acid glutamine by condensation of ornithine and carbamyl phosphate in an enzymatic reaction by ornithine carbamyl-transferase (Curis, Crenn, & Cynober, 2007; Kamoun, Rabier, Bardet, & Parvy, 1991), and 2) from the conversion of L-arginine to nitric oxide in a reaction catalyzed by nitric oxide synthase (NOS) enzymes (Aguilo et al., 2000). Importantly, oral L-citrulline (Curis et al., 2007; Osowska, Moinard, Neveux, Loi, & Cynober, 2004), unlike L-arginine (Luiking, Engelen, & Deutz, 2010; Luiking et al., 2008), bypasses hepatic and intestinal metabolism while remaining unaffected by arginase enzymes, thus allowing it to be transported to the kidneys where approximately 80% of L-citrulline is catabolized by the cells of the proximal tubules (van de Poll, Soeters, Deutz, Fearon, & Dejong, 2004). Furthermore, malate is an intermediate of tricarboxylic acid cycle and its supplementation may augment aerobic energy production (Bendahan et al., 2002; Wagenmakers, 1998). This is accomplished by malate's shuttle like action mitigating lactic acid production by allowing continued pyruvate production for energy utilization. Therefore, the beneficial effects of citrulline-malate may actually be attributed to the synergistic combination of both L-citrulline and malate in the muscle at the cellular metabolic level. In particular, an increased rate of adenosine triphosphate (ATP) production during exercise, followed by an increased recovery rate of phosphocreatine during the postexercise period (Bendahan et al., 2002) may be responsible. Also, increased bicarbonate reabsorption coupled with mitigating lactic

TABLE 1. Anthropometric Characteristics of the Subjects Used in the Study

Age (y)	Height (m)	Body mass (kg)	Body fat (%)
23.3 ± 1.5	1.79 ± 0.07	87.8 ± 9.1	16.4 ± 4.5

Data are presented as mean ± *SD* (*n* = 14).

acid accumulation may contribute to the antifatigue properties of citrulline-malate (Callis, Magnan de Bornier, Serrano, Bellet, & Saumade, 1991). These metabolic effects of oral citrulline-malate on muscle metabolism have been documented using P magnetic resonance spectroscopy (MRS) (Bendahan et al., 2002).

To date, only one published study investigated the potential ergogenic benefit of supplemental citrulline-malate ingestion (Perez-Guisado & Jakeman, 2010) on resistance exercise. The aforementioned study conducted the experimental trials across six gyms, and this may have limited the researchers to only reporting muscle performance using noninvasive techniques. Therefore, the aim of this study was to investigate the effects of supplemental citrulline-malate ingestion during repeated bouts of upper-body resistance exercise in a controlled laboratory setting. Furthermore, blood lactate and cardiovascular dynamics were measured. Based on citrulline-malate's chemical composition and prior studies utilizing human (Bendahan et al., 2002; Perez-Guisado & Jakeman, 2010) and animal models (Luiking et al., 2008; Wijnands et al., 2012), we hypothesized that citrulline-malate supplementation would enhance the work performed during repeated bouts of exhaustive resistance exercise.

MATERIALS AND METHODS

Subjects

Fourteen resistance-trained males enrolled at the University where the investigation was performed, volunteered for the study. Prior to the investigation, subjects completed a health history questionnaire and signed a statement of informed consent. To qualify for this study, subjects were classified as low-risk individuals as categorized by the American College of Sports Medicine (American College of Sports Medicine., Thompson, Gordon, & Pescatello, 2010) risk stratification, and the subject had to be able to perform 10 unassisted chin-ups with a 1-sec pause between repetitions. Also, subjects indicated that they had completed a minimum of 12 months of continuous recreational resistance exercise training for no less than three days a week at a medium to high training stress. The exclusion criteria of the study included: (a) musculoskeletal problems, (b) metabolic disorders, (c) cardiorespiratory ailments, (d) blood disorders, (e) history of psychological disorders, (f) use of tobacco products, (g) consuming more than 10 alcoholic beverages per week, (h) taking medication (prescription and/or nonprescription), and (i) taking supplements and/or use or prior use of anabolic steroids. All experimental procedures were reviewed and approved by the Institutional Review Board prior to the initiation of the study. Descriptive characteristics for the subjects are presented in Table 1.

Experimental Design

This study was designed as a randomized counterbalanced, double-blind experiment. The protocol employed in this study was based on a prior study (Greer & Jones, 2011), which tested the efficacy of arginine supplementation on resistance training performance. Subjects reported to the laboratory three times (i.e., visit 1, visit 2, and visit 3) at the same time of day. Visit 1 was used to obtain anthropometric data and to familiarize the subjects with the experimental protocol. During visit 2, half of the subjects chosen at random ingested a citrulline-malate (CM) solution and the other half consumed a placebo (PL) solution 1 hr prior to the exercise protocol. On visit 3, subjects consumed the other solution and performed the same exercise protocol. There was a 7-day period between visit 1 to visit 2, and between visit 2 to visit 3, which allowed ample time for full muscle recovery and served as a washout period between treatments.

Supplementation

Over-the-counter pharmaceutical grade CM (99% pure with no fillers, excipients, flavors, sweeteners; NutraBio Inc., Middlesex, New Jersey) or a PL mix of maltodextrin and aspartame (Merisant US, Inc., Chicago, Illinois) were mixed with 250 ml of Crystal Light lemonade (Kraft Foods Global Inc., Northfield, Illinois) and provided to subjects 60 min prior to performing the exercise protocol. The present dosage of CM (8 g) was selected based on a prior study that reported an ergogenic effect during multiple bouts of upper-body resistance training (Perez-Guisado & Jakeman, 2010). The PL was similar in color, smell, taste, and volume to the supplement. Subjects wore a nose clip during ingestion of both treatments (CM and PL) to further mitigate their sense of smell and taste.

Visit 1

This session was used to determine subjects' anthropometric data. Subjects were instructed to refrain from strenuous exercise and exhaustive labor for the upper-body (72 hr) and lower-body (48 hr) prior to each trial. Also, caffeine and alcohol intake were prohibited 48 hr before each of the following two visits. Furthermore, subjects were asked to maintain a log of their dietary intake 24 hr prior to visit 2 and were instructed to duplicate the nutritional intake prior to visit 3. Physical activity log was required for a 72 hr period. In addition, subjects performed a mock sub-maximal session to confirm meeting the inclusion criteria (10 unassisted chin-ups) and to familiarize themselves with the experimental procedures and equipment.

Visit 2 and 3 and Exercise Protocol

Subjects reported to the laboratory at their prescheduled time and prepared for testing. Upon arrival, they were questioned about their compliance in regards to their activity level and submitted their training and nutritional journal. Subjects kept their training schedule as consistent as possible over the course of the experiment and closely replicated their nutritional intake. All subjects met the pretesting guidelines required for participation and completed their scheduled sessions. Following the evaluator's review and approval of the compliance guidelines, subjects ingested either CM or a PL beverage and then rested quietly for 1 hr. Next, subjects

completed three sets each of chin-ups (hands pronated; Bodymasters Inc., Rayne, Louisiana, USA), reverse chin-ups (hands supinated; Bodymasters Inc., Rayne, Louisiana, USA), and push-ups (in the listed order) to failure with 3 min of rest between each set. Subjects began the exercise on a “go” command at the initial hanging position with full elbow extension for each chin-up or reverse chin-up repetition. Failure was defined as an inability of the subjects’ chin to reach parallel with the bar and undue swinging of the body. Markings on the chin-up and reverse chin-up apparatus ensured that each subject maintained the same hand placement during each visit and set. Next, subjects were instructed to do pushups at a pace set by a metronome, and a pause greater than 2 sec was cause for that set’s termination (failure). Push-ups repetitions were counted if the subject’s chest touched the tester’s fist resting on the mat, and the elbows returned to a fully extended position. The order of the exercises was the same for all subjects completing this investigation. Seven days later the subjects consumed the other beverage and repeated the identical protocol.

Cardiovascular Dynamics and Blood Analyses

Blood pressure and heart rate were measured at rest (pre-exercise), and min 5 and 10 of recovery following the completion of the exercise protocol (postexercise) by using an automated instrument (SunTech Medical, Morrisville, NC). Also, a single-use lancet device was used to puncture the skin just off the center of the finger pad. The first flow of blood was wiped away, and then approximately 5 μ l (2 mm) of blood was loaded on the lactate strip and immediately analyzed using the Lactate Pro Analyzer (ARKRAY Inc., Japan). Blood lactate concentrations were determined at rest (pre-exercise) and immediately after the completion of the exercise protocol (postexercise).

Statistical Analyses

Dietary recall data were compiled using Nutribase 7 (Clinical Edition; Cypersoft, Inc.; Arizona, USA) and analyzed using paired *t*-tests to assess differences between the CM and PL conditions. All other data were analyzed using PASW Statistics 22 (SPSS, Inc., Chicago, IL). Data for chin-ups, reverse chin-ups, and push-ups repetitions were analyzed by using a 2 (condition; citrulline malate and placebo) \times 3 (SET; 1, 2, and 3) repeated measures analysis of variance followed by Bonferroni adjustments to determine differences between groups. Paired *t*-tests were used to determine significant differences for total repetitions (set 1 + set 2 + set 3) per exercise (chin-ups, reverse chin-ups, and push-ups). Data for blood lactate were analyzed by using a 2 (condition; citrulline malate and placebo) \times 2 (time; baseline and postexercise) repeated measures analysis of variance followed by Bonferroni adjustments to determine differences between groups. Data for heart rate, systolic blood pressure, and diastolic blood pressure were analyzed by using a 2 (condition; citrulline malate and placebo) \times 3 (time; baseline, 5 min postexercise, and 10 min postexercise) repeated measures analysis of variance followed by Bonferroni adjustments to determine differences between groups. Statistical significance difference was established at $p < .05$. Data are reported as mean \pm standard deviation.

TABLE 2. Dietary Analyses

Carbohydrate (g)		Fat (g)		Protein (g)		Calories (kcal)		L-arginine (mg)	
Placebo	Citrulline malate	Placebo	Citrulline malate	Placebo	Citrulline malate	Placebo	Citrulline malate	Placebo	Citrulline malate
190 ± 29	188 ± 31	58 ± 21	59 ± 19	103 ± 36	103 ± 38	1727 ± 412	1729 ± 407	1843 ± 439	1850 ± 445

Data are presented as mean ± SD.

No significant ($p > 0.05$) differences were detected between groups.

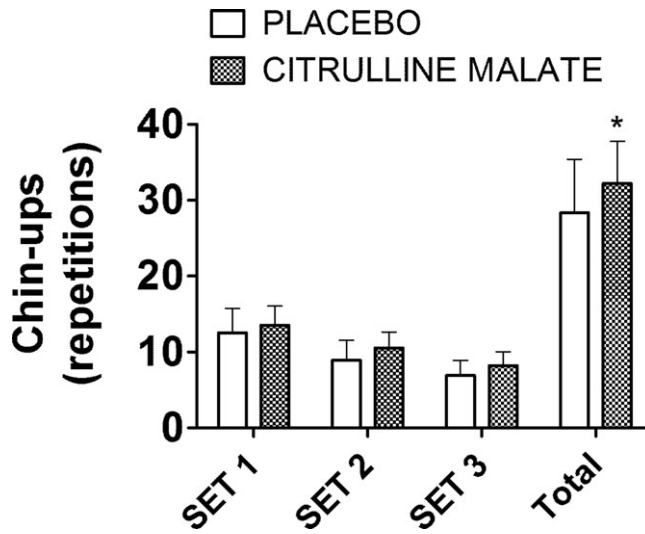


FIGURE 1. Number of chin-ups repetitions. * indicates $p = .003$ between citrulline-malate (CM) and placebo (PL) for total repetitions.

RESULTS

Analysis of dietary recall information indicated no differences in total calorie intake, macronutrient, or the selected amino acid intake in the 24 hr preceding the CM or PL treatment. Table 2 provides a summary of the dietary analysis prior to each session.

Analyses of performance on the resistance exercises (chin-ups, reverse chin-ups, and push-ups) indicated similar responses across all three exercises. The sum of three sets for each exercise treatment indicated a significant effect for condition (chin-ups: PL = 28.4 ± 7.1 , CM = 32.2 ± 5.6 , $p = .003$, Cohen's $d = .606$; reverse chin-ups: PL = 26.6 ± 5.6 , CM = 32.1 ± 7.1 , $p = .017$, Cohen's $d = .860$; push-ups: PL = 89.1 ± 37.4 , CM = 97.7 ± 36.1 , $p < .001$, Cohen's $d = .235$), with the CM condition resulting in greater number of repetitions performed in each exercise (Figures 1–3). Additionally, all three resistance exercises also indicated a significant effect for time (chin-ups: $p < .001$, partial $\eta^2 < .869$; reverse chin-ups: $p < .001$, partial $\eta^2 < .820$; and push-ups: $p < .001$, partial $\eta^2 < .811$), with the number of repetitions performed in both the CM and PL conditions decreasing from set 1 to set 3 (Figures 1–3).

Blood lactate data suggest a time effect (pre-exercise: PL = 1.3 ± 0.4 , CM = 1.3 ± 0.3 mmol/l; postexercise: PL = 9.7 ± 2.2 , CM = 9.7 ± 1.2 mmol/l, $p < .001$, partial $\eta^2 = .960$), but no treatment differences ($p = .935$, partial $\eta^2 < .001$) (Figure 4).

Heart rate was measured as an indicator of exercise intensity and to document that subjects in both groups exerted similar effort following CM and PL supplementation. Heart rate data suggest a time effect (pre-exercise: PL = 69.9 ± 13.3 , CM = 69.4 ± 14.8 bpm; 5 min postexercise: PL = 100.1 ± 16.5 , CM = 95.9 ± 11.8 bpm; 10 min postexercise: PL = 98.8 ± 17.8 , CM = 93.6 ± 11.7 bpm, $p < .001$, partial $\eta^2 = .841$), but no treatment differences ($p = .512$, partial $\eta^2 < .017$) (Figure 5).

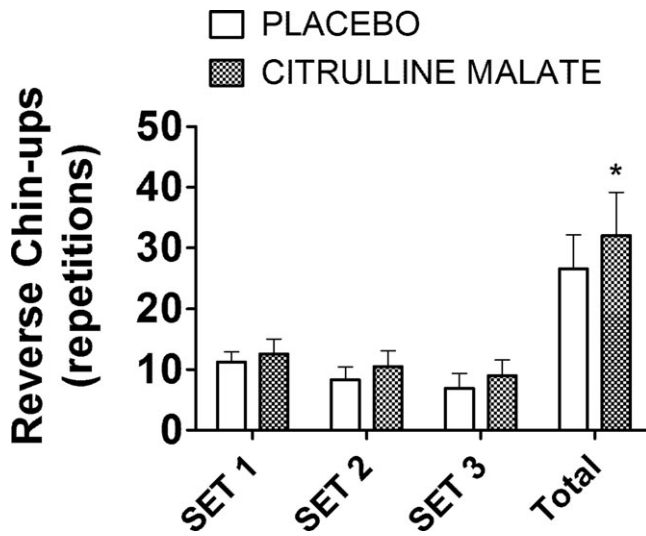


FIGURE 2. Number of reverse chin-ups repetitions. * indicates $p = .017$ between citrulline-malate (CM) and placebo (PL) for total repetitions.

Systolic BP data did not suggest differences for time ($p = .078$, partial $\eta^2 = .093$) or treatment ($p = .119$, partial $\eta^2 = .091$). Diastolic BP data did not indicate differences for time ($p = .069$, partial $\eta^2 = .098$), but suggest treatment differences ($p = .014$, partial $\eta^2 = .212$), where subjects that ingested CM had lower diastolic BP (Figure 6).

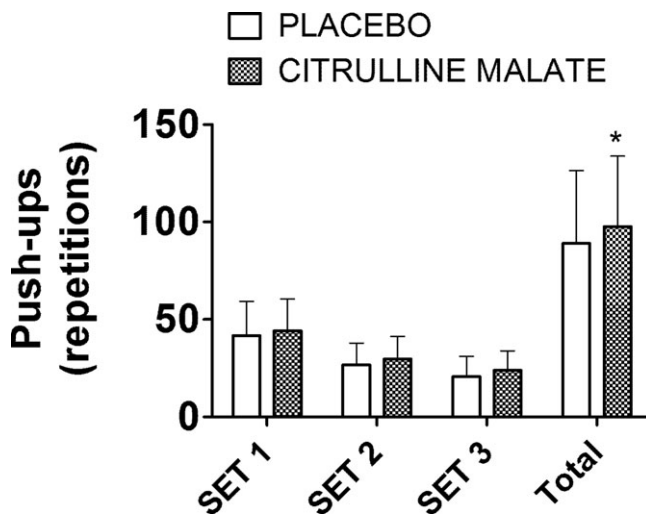


FIGURE 3. Number of push-ups repetitions. * indicates $p < .001$ between citrulline-malate (CM) and placebo (PL) for total repetitions.

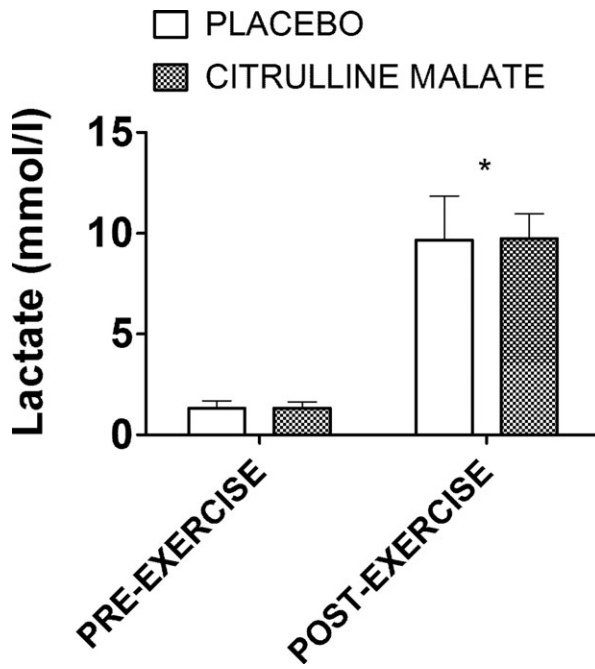


FIGURE 4. Blood lactate (mmol/l). * indicates $p < .001$ between pre-exercise and postexercise.

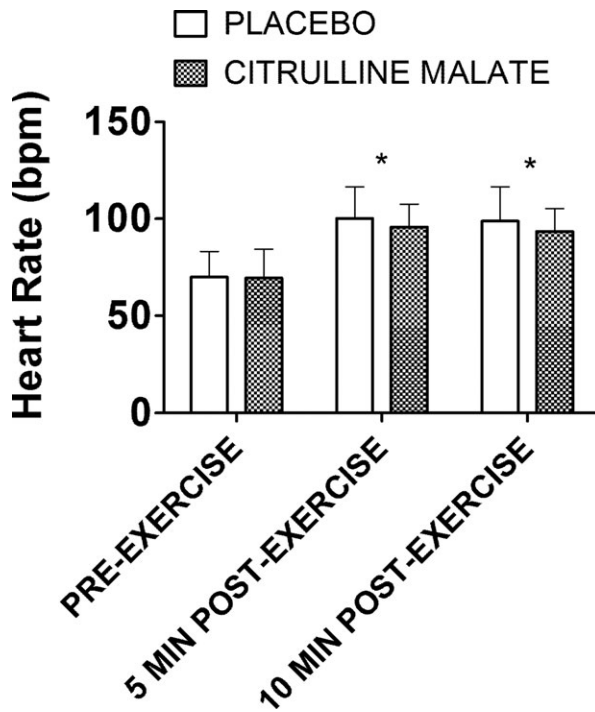


FIGURE 5. Heart rate (beats per minute; bpm). * indicates $p < .001$ between pre-exercise and 5 and 10 min postexercise.

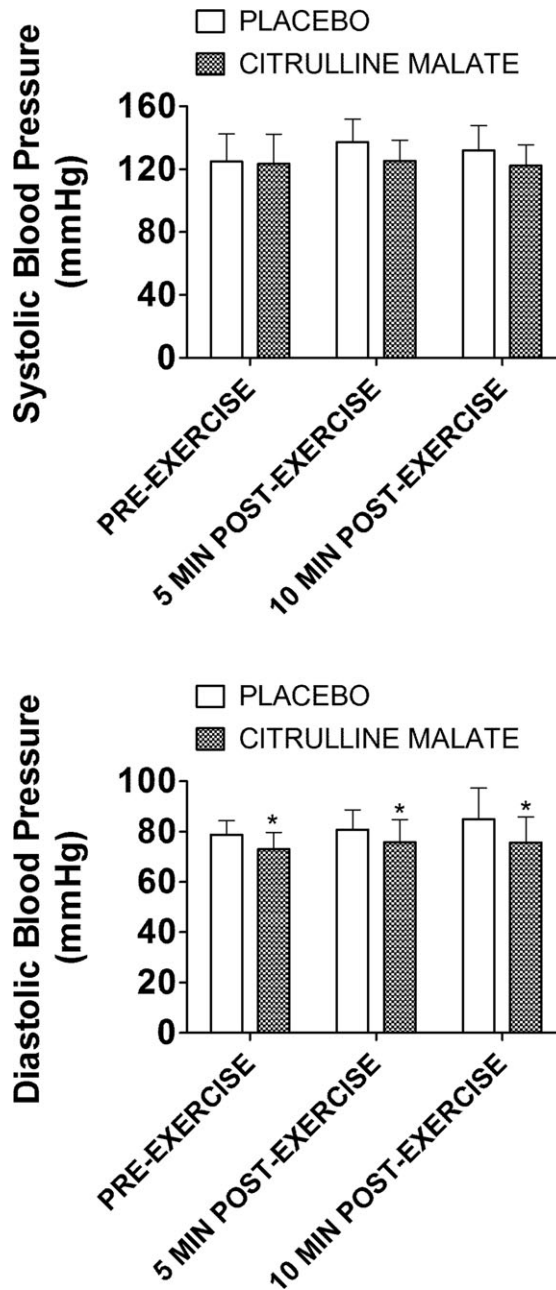


FIGURE 6. Systolic and diastolic blood pressures (mmHg). * indicates $p = .014$ between citrulline-malate (CM) and placebo (PL).

DISCUSSION

In the current study, we hypothesized that citrulline-malate supplementation prior to an upper-body resistance protocol would augment resistance exercise performance (i.e., number of repetitions performed). Our results suggest that subjects

who consumed the citrulline-malate treatment performed more repetitions during the selected exercises, respectively; however, there were no significant differences in the individual sets within each exercise between the treatments.

The present results are in agreement with a prior study that investigated the effects of citrulline-malate supplementation on resistance exercise performance. Specifically, Perez-Guisado and Jakeman reported that a single dose of citrulline-malate (8 g) increased performance by an average of 19%, measured as the number of repetitions performed until exhaustion occurred (Perez-Guisado & Jakeman, 2010). In the current investigation, subjects increased overall repetitions performed in chin-ups, reverse chin-ups, and push-ups.

The precise mechanism attributed to citrulline-malate's potential ergogenic effect remains obscure, but most nitric oxide stimulating supplements rest on the assumption of nitric oxide stimulation. Nitric oxide is a molecule that plays an important role in many bodily functions including vasodilatation, blood flow, and mitochondrial respiration (Petrovic et al., 2008). Additionally, nitric oxide regulates glucose uptake and oxidation, mitochondriogenesis, and other contractile functions in skeletal muscle (Petrovic et al., 2008). Availability of plasma arginine to endothelial cells is a limiting factor for NO synthesis (Nussler, Billiar, Liu, & Morris, 1994). Citrulline supplementation increases levels of plasma L-arginine (Hickner et al., 2006); thereby, augmenting plasma arginine concentrations following exercise (Goodwin, Solomonson, & Eichler, 2004; Mori, 2007). Finally, malate affects oxidative ATP production through anaplerotic reactions (Gibala et al., 2000), which mitigates ammonia's blockade of the oxidative pathway, therefore allowing continued pyruvate genesis (lactate \leftrightarrow pyruvate). However, in the current study while blood lactate concentrations increased significantly following our upper-body protocol in both treatments, we did not detect any differences between the citrulline-malate and placebo trials. Therefore, based on our findings we infer that citrulline-malate's ergogenic properties are not attributed to any alterations in acid base balance.

Finally, an acute bout of resistance exercise can significantly increase heart rate and blood pressure (Fleck & Dean, 1987), especially if the valsalva maneuver is utilized (Kraemer et al., 2000). The magnitude of this response is directly related to the intensity and volume of exercises performed, muscle mass utilized during the protocol, recovery period between bouts of exercise, and contraction velocity especially during the first 5 sec after completing a bout of resistance exercise (Ratamess et al., 2007). The current protocol utilized the upper-body musculature, incorporating nine total sets to failure with 3-min recovery periods between bouts of exercise. Specifically, blood pressure was monitored during the recovery period following the exercise session. In light of the aforeindicated metabolic reactions, citrulline-malate supplementation has been reported to decrease blood pressure in patients with hypertension and heart failure (Orozco-Gutierrez et al., 2010; Pertierra et al., 2001; Smith et al., 2006); however, the data in the current study generally contradict these findings in healthy male subjects. It is important to note that diastolic blood pressure was lower in the citrulline-malate treatment in the present study. This may be attributed to oral citrulline being a nitric oxide precursor via arginine thus causing vasodilation; however, more research is needed before any practical implications may be inferred. Future studies should expand the

monitoring of blood pressure for an extended period during the recovery period. It should be noted that prior studies utilizing cardiovascular patients implemented a daily loading phase extending beyond a 30-day period, while the current investigation used an acute dose. Furthermore, subjects in the aforementioned studies had some form of cardiovascular disease, while subjects in the current investigation were free of any medical conditions.

In closing, there are general limitations in the current study. First, nitric oxide measurements were not ascertained in the present investigation; thereby, rendering further theoretical speculation, not scientific data. Second, subjects' meals were not provided and may not accurately reflect exact food consumption; however, we did encourage subjects to duplicate intakes for 24 hr preceding each trial. Finally, no college-age resistance-trained females were included in this investigation, which limits the current investigation findings from being generalized to this population. However, the findings of this study support continued investigations exploring the effects of citrulline-malate on various populations, training paradigms, and metabolic mechanisms during resistance training exercise.

CONCLUSIONS

In conclusion, a specific resistance protocol was used in this study to investigate the effects of citrulline-malate supplementation on exercise performance in college-age resistance-trained males. Collectively, our data suggest that citrulline-malate increases work performed during upper body resistance exercise. Thus, our data suggest that citrulline-malate ingestion before resistance exercise might help increase the training volume of resistance-trained college-age males. Further studies are warranted exploring various populations and training paradigms.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article. Use of trade names does not constitute endorsement of product. The results of the present study do not constitute endorsement by the Journal of Dietary Supplements. No external funding was received to conduct this study.

REFERENCES

- Aguilo A, Castano E, Tauler P, Guix MP, Serra N, Pons A. Participation of blood cells in the changes of blood amino acid concentrations during maximal exercise. *J Nutr Biochem*. 2000;11(2):81–86.
- Alvares TS, Meirelles CM, Bhambhani YN, Paschoalin VM, Gomes PS. L-Arginine as a potential ergogenic aid in healthy subjects. *Sports Med*. 2011;41(3):233–248. doi: 10.2165/11538590-000000000-00000
- Thompson WR, Gordon NF, Pescatello LS; American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription (8th ed.). Philadelphia: Lippincott Williams & Wilkins, 2010.
- Barbul A. Arginine: biochemistry, physiology, and therapeutic implications. *J Parenter Enteral Nutr*. 1986;10(2):227–238.
- Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, Cozzone PJ. Citrulline/malate promotes aerobic energy production in human exercising muscle. *Br J Sports Med*. 2002;36(4):282–289.

- Bescos R, Sureda A, Tur JA, Pons A. The effect of nitric-oxide-related supplements on human performance. *Sports Med.* 2012;42(2):99–117. doi: 10.2165/11596860-000000000-00000
- Briand J, Blehaut H, Calvayrac R, Laval-Martin D. Use of a microbial model for the determination of drug effects on cell metabolism and energetics: study of citrulline-malate. *Biopharm Drug Dispos.* 1992;13(1):1–22.
- Callis A, Magnan de Bornier B, Serrano JJ, Bellet H, Saumade R. Activity of citrulline malate on acid–base balance and blood ammonia and amino acid levels. Study in the animal and in man. *Arzneimittelforschung.* 1991;41(6):660–663.
- Creff A. Controlled double-blind clinical-study against stimol placebo in the treatment of asthenia. *Gazette Med De France.* 1982;89:1926–1929.
- Curis E, Creonn P, Cynober L. Citrulline and the gut. *Curr Opin Clin Nutr Metab Care.* 2007;10(5):620–626. doi: 10.1097/MCO.0b013e32829fb38d
- Eichner ER. Ergolytic drugs in medicine and sports. *Am J Med.* 1993;94(2):205–211.
- Elam RP, Hardin DH, Sutton RA, Hagen L. Effects of arginine and ornithine on strength, lean body mass and urinary hydroxyproline in adult males. *J Sports Med Phys Fitness.* 1989;29(1):52–56.
- Fahs CA, Heffernan KS, Fernhall B. Hemodynamic and vascular response to resistance exercise with L-arginine. *Med Sci Sports Exerc.* 2009;41(4):773–779. doi: 10.1249/MSS.0b013e3181909d9d
- Fleck SJ, Dean LS. Resistance-training experience and the pressor response during resistance exercise. *J Appl Physiol (1985).* 1987;63(1):116–120.
- Fricke O, Baecker N, Heer M, Tuttlewski B, Schoenau E. The effect of L-arginine administration on muscle force and power in postmenopausal women. *Clin Physiol Funct Imaging.* 2008;28(5):307–311. doi: 10.1111/j.1475-097X.2008.00809.x
- Gibala MJ, Young ME, Taegtmeier H. Anaplerosis of the citric acid cycle: role in energy metabolism of heart and skeletal muscle. *Acta Physiol Scand.* 2000;168(4):657–665. doi: 10.1046/j.1365-201x.2000.00717.x
- Goodwin BL, Solomonson LP, Eichler DC. Argininosuccinate synthase expression is required to maintain nitric oxide production and cell viability in aortic endothelial cells. *J Biol Chem.* 2004;279(18):18353–18360. doi: 10.1074/jbc.M308160200
- Goubel F, Vanhoutte C, Allaf O, Verleye M, Gillardin JM. Citrulline malate limits increase in muscle fatigue induced by bacterial endotoxins. *Can J Physiol Pharmacol.* 1997;75(3):205–207.
- Greer BK, Jones BT. Acute arginine supplementation fails to improve muscle endurance or affect blood pressure responses to resistance training. *J Strength Cond Res.* 2011;25(7):1789–1794. doi: 10.1519/JSC.0b013e3181e07569
- Hickner RC, Tanner CJ, Evans CA, Clark PD, Haddock A, Fortune C, Geddis H, Waugh W, McCammon M. L-citrulline reduces time to exhaustion and insulin response to a graded exercise test. *Med Sci Sports Exerc* 38: 660–666, 2006.
- Kamoun P, Rabier D, Bardet J, Parvy P. Citrulline concentrations in human plasma after arginine load. *Clin Chem.* 1991;37(7):1287.
- Kraemer WJ, Ratamess N, Fry AC, Triplett-McBride T, Koziris LP, Bauer JA, . . . Fleck SJ. Influence of resistance training volume and periodization on physiological and performance adaptations in collegiate women tennis players. *Am J Sports Med.* 2000;28(5):626–633.
- Little JP, Forbes SC, Candow DG, Cornish SM, Chilibeck PD. Creatine, arginine alpha-ketoglutarate, amino acids, and medium-chain triglycerides and endurance and performance. *Int J Sport Nutr Exerc Metab.* 2008;18(5):493–508.
- Luiking YC, Engelen MP, Deutz NE. Regulation of nitric oxide production in health and disease. *Curr Opin Clin Nutr Metab Care.* 2010;13(1):97–104. doi: 10.1097/MCO.0b013e328332f99d
- Luiking YC, Hallemeesch MM, van de Poll MC, Dejong CH, de Jonge WJ, Lamers WH, Deutz NE. Reduced citrulline availability by OTC deficiency in mice is related to reduced nitric oxide production. *Am J Physiol Endocrinol Metab.* 2008;295(6):E1315–E1322. doi: 10.1152/ajpendo.00055.2008
- Mori M. Regulation of nitric oxide synthesis and apoptosis by arginase and arginine recycling. *J Nutr.* 2007;137(6 Suppl 2):1616S-1620S.

- Nussler AK, Billiar TR, Liu ZZ, Morris SM, Jr. Coinduction of nitric oxide synthase and argininosuccinate synthetase in a murine macrophage cell line. Implications for regulation of nitric oxide production. *J Biol Chem.* 1994;269(2):1257–1261.
- Orozco-Gutierrez JJ, Castillo-Martinez L, Orea-Tejeda A, Vazquez-Diaz O, Valdespino-Trejo A, Narvaez-David R, . . . Sanchez-Santillan R. Effect of L-arginine or L-citrulline oral supplementation on blood pressure and right ventricular function in heart failure patients with preserved ejection fraction. *Cardiol J.* 2010;17(6):612–618.
- Osovska S, Moinard C, Neveux N, Loi C, Cynober L. Citrulline increases arginine pools and restores nitrogen balance after massive intestinal resection. *Gut.* 2004;53(12):1781–1786. doi: 10.1136/gut.2004.042317
- Perez-Guisado J, Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. *J Strength Cond Res.* 2010;24(5):1215–1222. doi: 10.1519/JSC.0b013e3181cb28e0
- Perticone F, Ceravolo R, Pujia A, Ventura G, Iacopino S, Scozzafava A, . . . Schillaci G. Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation* 2001;104(2), 191–196.
- Petrovic V, Buzadzic B, Korac A, Vasilijevic A, Jankovic A, Micunovic K, Korac B. Antioxidative defence alterations in skeletal muscle during prolonged acclimation to cold: role of L-arginine/NO-producing pathway. *J Exp Biol.* 2008;211(Pt 1):114–120. doi: 10.1242/jeb.012674
- Ratamess NA, Falvo MJ, Mangine GT, Hoffman JR, Faigenbaum AD, Kang J. The effect of rest interval length on metabolic responses to the bench press exercise. *Eur J Appl Physiol.* 2007;100(1):1–17. doi: 10.1007/s00421-007-0394-y
- Smith HA, Canter JA, Christian KG, Drinkwater DC, Scholl FG, Christman BW, . . . Summar ML. Nitric oxide precursors and congenital heart surgery: a randomized controlled trial of oral citrulline. *J Thorac Cardiovasc Surg.* 2006;132(1):58–65. doi: 10.1016/j.jtcvs.2006.02.012
- van de Poll MC, Soeters PB, Deutz NE, Fearon KC, Dejong CH. Renal metabolism of amino acids: its role in interorgan amino acid exchange. *Am J Clin Nutr.* 2004;79(2):185–197.
- Wagenmakers AJ. Protein and amino acid metabolism in human muscle. *Adv Exp Med Biol.* 1998;441:307–319.
- Wijnands KA, Vink H, Briede JJ, van Faassen EE, Lamers WH, Buurman WA, Poeze M. Citrulline a more suitable substrate than arginine to restore NO production and the microcirculation during endotoxemia. *PLoS One.* 2012;7(5):e37439. doi: 10.1371/journal.pone.0037439
- Wilcock IM, Cronin JB, Hing WA. Physiological response to water immersion: a method for sport recovery? *Sports Med.* 2006;36(9):747–765.
- Williams MH. Facts and fallacies of purported ergogenic amino acid supplements. *Clin Sports Med.* 1999;18(3):633–649.