Journal of Strength and Conditioning Research Publish Ahead of Print
DOI: 10.1519/JSC.0000000000002356

Title:
The effect of citrulline malate supplementation on muscle fatigue among healthy participants

Running Title:
Citrulline malate and muscle fatigue

Authors:
Tyler M. Farney*
Matthew V. Bliss
Christopher M. Hearon
Dassy A. Salazar

Affiliation and Location of Work:
Human Performance Laboratory
Department of Health & Kinesiology
Texas A&M University – Kingsville
Kingsville, TX 78363

* Corresponding Author Contact:
Tyler M. Farney, Ph.D., CSCS, USAW
700 University Blvd (MSC 198)
Kingsville, TX 78363
Office: (361)-593-3213
Email: Tyler.Farney@tamuk.edu

Funding
No external funding was received to support the current investigation.

Conflict of Interest
No conflict of interest is declared for any author in relation to this work.

ABSTRACT

The focus of the investigation was to examine the effects of citrulline malate on muscular fatigue in healthy, recreationally trained participants. Twelve participants (males = 6; females = 6) (24.1 ± 3.9 yrs) visited the lab on three separate days all separated by one week. Each visit consisted of consuming one of three treatments: placebo (PLA), citrulline malate (8 g) (CM), and control (CON) in which no drink mixture was consumed. For each day of testing, participants consumed assigned treatment and performed one high-intensity exercise trial consisting of squats, lunge jumps, squat jumps, and lateral jumps. Participants performed the exercises in the listed order, which was designated as one round. Each participant performed 3 rounds, with the work to rest ratio being 20 sec work, 30 sec rest. A one min rest was given between rounds. A pre/post-exercise isokinetic leg extension test was performed to measure for peak power, peak torque, and rate of fatigue. Additionally, blood lactate was obtained pre/post-exercise. There were no treatment or interaction effects ($p > 0.05$) for peak torque, peak power, rate of fatigue, or blood lactate accumulation. However, there was a statistical significant decrease from pre/post-ex for peak torque ($p = 0.003$), peak power ($p = 0.003$), and rate of fatigue ($p = 0.001$). Additionally, lactate accumulation did increase significantly from pre/post-ex ($p = 0.0001$). Lastly, neither total work nor final heart rate was statistical significant between the treatments ($p > 0.05$). Citrulline malate was not effective in improving performance or alleviating fatigue following a high-intensity exercise session.

Key words: Fatigue; power/force; high-intensity exercise; lactate; ergogenic aid

INTRODUCTION

Within the last few years, citrulline malate (CM) has been gaining attention for its ability to inhibit fatigue and enhance skeletal muscle power output via the decline in metabolic by-product reduction. Citrulline malate is composed of the non-essential amino acid citrulline and malate, a Krebs cycle intermediate. When taken together, CM has been shown to enhance a greater oxidative energy turnover and lower power/pH ratio (4), which in turn will lower the ATP cost of muscle force production (8). Studies have reported CM to enhance aerobic energy production (4), augment muscular force output (15), alleviate muscle fatigue (4), and improve performance during lower-body resistance exercise (22).

The exact mechanisms of how CM works on alleviating fatigue are unknown, however, the idea is that since citrulline is one of the amino acids of the ureagenesis cycle, an excess availability will help with the facilitation of ammonia clearance. An accumulation of intracellular ammonia stimulates glycolysis while blocking the aerobic utilization of pyruvate (20). The subsequent effect is then a switch in energy metabolism toward the exclusive formation of lactate (15). As for malate, its primary role is that of a metabolic intermediate of the Krebs cycle, as well as having the capability of behaving as a metabolic shuttle between the cytoplasm and mitochondria (20). This capability of being a metabolic shuttle enables the blockade of the oxidative system to be bypassed, thus, ensuring a greater oxidative energy turnover (4). A greater oxidative capacity ensures a lower formation of lactate, thus, alleviating the development of muscular fatigue. Therefore, based upon the physiology of CM, supplementing could be beneficial in lowering ammonia accumulation and preserving force production during time of importance, such as athletic competition.

Another promoted ergogenic benefit of CM supplementation is the ability to increase nitric oxide (NO) by increasing L-arginine concentrations (5, 17). Nitric oxide has many physiological roles, however, it is best known to be an important vasodilator during exercise (19). Hickner et al. has reported that the inhibition of NO synthase decreases local skeletal muscle blood flow during exercise (9), while others have demonstrated a reduced maximal oxygen consumption when NO synthase was inhibited (12). To increase NO production, many have tried to supplement with L-arginine due to NO being synthesized from L-arginine via the NO synthase (11). However, despite infusing with L-arginine, local muscle blood flow has been shown to be unaltered (9), thus, brings to the reason why L-citrulline has become popular with blood flow changes. L-citrulline supplementation has been shown to increase L-arginine concentrations to a higher level than oral L-arginine administration (10), with over 80% of L-citrulline being recycled to L-arginine in endothelial cells to produce NO (16). Taken together, CM supplementation may help to increase O_2 delivery to working muscle. This in turn will help alleviate fatigue through the clearance of metabolic waste products, which accumulate during times of high-intensity exercise.

Notwithstanding the claims of the promoted benefits of CM supplementation, acute ingestion of CM still remains controversial (5). For example, Cutrufello and colleagues reported that 6 g of citrulline consumed 1-2 hrs before exercise was ineffective in altering the anaerobic threshold or time to exhaustion during a graded exercise test (6). Also, the authors reported that CM did not improve the total number of upper-body repetitions of the chest press at 80% of participant one-repetition maximum (1RM) (6). In another study performed by Cunniffe et al., participants consumed 12 g of CM 60 min prior to repeat maximal cycle sprints (10 x 15 s; 30 s recovery), and had no significant impact upon power fatigue index or acid-base balance (5). Additionally,

others have reported a reduction in time to exhaustion during a graded treadmill test following 3-9 g of CM taken 3-24 hrs before testing (10). On the other hand, Wax et al. found that CM may be beneficial in improving exercise performance during lower-body multiple-bout resistance exercise (22). Within the Wax investigation, participants performed five sequential sets at 60% 1RM to failure on the leg press, hack squat, and leg extension. Although the exercise protocol resulted in a significant decrease of repetitions, the CM group performed significantly higher number of repetitions for all three exercises compared to a placebo group (22). Discrepancies amongst the literature can be accounted for by the differences in dosages (3 g-12 g), dosage timing (acute vs chronic supplementation; 60 min-120 min prior to exercise), and/or exercise modalities (resistance exercise vs endurance exercise).

To our knowledge, no investigation has focused on muscle contractile properties such as power, torque, and rate of fatigue following high-intensity exercise, especially within major muscle groups such as the quadriceps. Investigations have used high-intensity exercise as a modality, however, no investigation has used a protocol that is commonly found amongst strength and conditioning/health practitioners. Based upon the notion of CM supplementation and its promoted effect upon metabolite accumulation, it was the purpose of this investigation was to examine the effects of CM upon muscle fatigue following high-intensity exercise. Additionally, this investigation also wanted to determine if heart rate and total work were improved following CM supplementation. Our hypothesis was that supplementing with CM would help to attenuate local muscle fatigue and improve contractile efficiency through the clearance of metabolite accumulation. An additional hypothesis was that supplementing with CM would allow for more work to be completed along with a lower HR during the high-intensity exercise.

METHODS

Experimental Approach to the Problem

The purpose of this investigation was to investigate if citrulline malate (CM) had an impact in alleviating muscle fatigue following a high-intensity exercise trial. In order to determine the impact of CM on fatigue, a single blind balanced cross-over design was used with each participant performing 3 experimental testing sessions after consuming one of the three treatments in a randomized order: 1) 8 g of a commercially available amino acid supplement (citrulline malate) (CM) mixed into 20 oz of sugar free flavored water, 2) a Placebo (PLA) containing 20 oz of sugar free flavored water with no CM, or 3) a Control (CON) containing no administration of a drink. The order of treatment consumption was randomized for all participants. All testing sessions were conducted on separate days with a one-week "wash-out" period for each treatment. For each of the testing sessions, all participants performed one high-intensity exercise protocol consisting of four exercises: squats, lunge jumps, squat jumps, and side-to-side jumps. All exercises were performed as fast as possible with as many reps within 20 sec. Participants wore a weighted vest for all testing sessions, with males wearing 40 lbs. of weight in the vest, and females wearing 20 lbs. of weight. To determine muscle fatigue, a fatiguing isokinetic leg extension test was performed both pre- and post-exercise. Additionally, a lactate sample was collected from each participant both prior to the leg extension test, and immediately following the high-intensity exercise session. The following variables were measured or derived for analysis within this investigation: rate of quadriceps fatigue, perceived local fatigue, relative muscular strength, total work, and lactate accumulation.

Participants

Twelve (males: n = 6; females: n = 6) recreationally trained adults (24.1 ± 3.9 yrs) participated in this study. In order to qualify to participate within this investigation, each participant had to have been involved in a structured exercise training program (including both aerobic and anaerobic) for the last six months, and be free from any knee/hip injuries. At the time of testing, none of the participants had any recent surgeries or knee/hip injuries, as well as none were pregnant or smokers. After explanation of the experimental procedures, all participants gave their written informed consent before study commencement which was approved by the local institutional review board. All participants underwent a health screening procedure according to the American College of Sports Medicines' Guidelines for Exercise Testing and Prescription. Prior to the beginning of the testing sessions, all participants were fully familiarized with the laboratory exercise testing procedures.

Procedures

Participants reported to the lab for a total of four visits. The first day of testing was considered the familiarization trial, and was done to determine if participants were able to sustain the protocol. Upon arriving to the laboratory, all participants were informed of all aspects of the study, giving written consent to participate, and a health screening to determine eligibility. During the familiarization trial, all participants performed both the pre/post-exercise isokinetic leg extension test, and the high-intensity exercise protocol. Additionally, all participants were fitted with the weighted vest to determine the appropriate amount of weight to be used for the subsequent three testing sessions. Males were originally fitted with 40 lbs. (which was the max the vest could contain), while females were fitted with 20 lbs. The weighted vest was set up so that 4 lb. increments could be removed to ensure participant completion of the high-intensity

exercise protocol. The subsequent three days of testing were considered the experimental trials, and all testing days were separated by a one-week. In addition to the pre/post-exercise isokinetic leg extension test and exercise protocol, lactate was collected pre/post-exercise.

Isokinetic Leg Extension Test

Participants performed an isokinetic leg extension test on a Biodex dynamometer to determine changes in peak power, peak torque, and rate of fatigue in the dominant quadriceps. Following a standardized five min warm-up via a cycle ergometer, participants were seated on the Biodex dynamometer with straps across the upper body and hips to ensure total isolation of the dominant quadriceps. While on the dynamometer, participants were adjusted so that the starting position for each participant was with the knee joint flexed, and the medial condyle of the working leg was centered with the attachment arm of the Biodex. For all experimental trials, and including the familiarization trial, participants begin the isokinetic test with no resistance for ten repetitions (reps). Upon completion of the warm-up set and following a ten sec rest, participants performed 15 maximal leg extensions. The maximal leg extensions were performed at a constant rate of $180°\cdot sec^{-1}$. This isokinetic leg extension test was performed both pre and post high-intensity exercise. Peak torque, peak power, and fatigue rate were used in data analysis. Fatigue rate was displayed as a percentage, and was derived by the difference between peak torque and lowest torque, divided by peak torque, and finally multiplied by 100 to get into a percentage.

High Intensity Exercise Protocol

Each participant performed three high-intensity exercise sessions, with each session consisting of four exercises: squats, lunge jumps, squat jumps, and lateral jumps. These exercises were selected due to the high contribution of the quadriceps muscles throughout each movement

Exercises began immediately following the pre isokinetic leg extension test. Participants were instructed to perform the exercises in the order listed above with the completion of all four exercise and rest times between each exercise being designated as a round. Each participant completed three rounds of exercises with a one min rest between each round. Upon completion of the three rounds, the post isokinetic leg extension test was performed. Each testing session consisted of performing each exercise for a period of 20 sec with a 30 sec rest between each exercise. All four exercises for each visit were performed wearing a weighted vest (composed of 10 - 4 lb. weights) (40 lb. for males; 20 lb. for females). Heart rate (HR) and the amount of reps completed were obtained for each exercise for each round. However, for data analysis, total amount of reps performed for the entire day of testing, and only the final HR at the completion of the protocol were included. Total amount of repetitions completed per testing session was referred to as total work. Lastly, blood lactate was recorded via a standard finger prick immediately before the pre isokinetic leg test, and immediately post high-intensity exercise.

The squats was performed by standing with feet shoulder width apart, and hands either behind the head or at the sides. From this point, participants began the movement by flexing the knees and hips until the upper leg was parallel with the ground. Once this position was achieved, participants quickly reversed position by extending both the knees and hips until the participant was in the original starting position. The lunge jumps were performed by starting off in a staggered position with one leg in the forward position, thigh parallel to the ground, and the opposite leg stepping backward up onto the ball of the foot. Participants then jumped and switched legs, ending with the opposite leg in the forward position. The jump squats were performed by starting off in the same position as the squats, with the initial start being the exact same in the eccentric portion of the movement. Once the participants lowered the body

downward into a regular squat, they jumped upward as explosively as possible. As the participants landed, they lowered their body back into the squat position to complete one rep. The lateral jumps were performed by starting off with feet hip-width apart, and sitting back into a shallow squat position. To begin, participants would slightly flex the knees, then jump explosively off both feet to either the right or left. Upon landing softly, the participants would immediately jump back to the other side.

Supplementation

Citrulline malate was the supplement investigated within this project. Participants consumed all treatments one hr prior to the pre-isokinetic leg extension test. All participants consumed three separate treatments on different days, in a randomized order, all separated by a one-week "wash-out" period. Treatments included: L-Citrulline DL-Malate (CM) (Bulk Supplements, Henderson, NV), placebo (PLA), and control (CON). The CM treatment contained 8 g of CM mixed into 20 oz of sugar free flavored water (Great Value, Wal-Mart Stores Inc, Bentonville, AR). The PLA treatment contained 20 oz of sugar free flavored water. The CON treatment contained no administration of a drink.

Data Analysis

Two-way (supplement x time) ANOVA with repeated measures was used to analyze for differences between trials (CM, PLA, CON) across time (pre-/post-exercise) for peak power, peak torque, fatigue rate, and lactate accumulation. A one-way (supplement) ANOVA with repeated measures was used to analyze for differences between trials (CM, PLA, CON) for final heart rate and total work completed. If needed, appropriate post-hoc tests were used to make all pairwise comparisons for specific differences across the three experimental trials and/or time points. The experiment wise error rate ($\alpha = 0.05$) was maintained throughout all post-hoc tests

for specific differences. Finally, a generalized eta squared following the equations of Bakeman was used for effect size determination (2).

RESULTS

All participants completed all aspects of this study. No significant main effects for supplement were observed ($p > 0.05$) for peak torque ($\eta^2 = 0.02$), peak power ($\eta^2 = 0.01$), rate of fatigue ($\eta^2 = 0.05$), blood lactate accumulation ($\eta^2 = 0.07$), final heart rate ($\eta^2 = 0.10$), or total reps completed ($\eta^2 = 0.08$) (Table 1).

As expected, there was a significant main effect for time where there was a decrease following the high-intensity exercise compared to pre-exercise for peak power ($p = 0.003$, $\eta^2 = 0.57$), and peak torque ($p = 0.003$, $\eta^2 = 0.57$) (Table 2), as well as a significant increase in fatigue rate for the isokinetic test ($p = 0.001$, $\eta^2 = 0.63$), and a significant increase in lactate accumulation ($p = 0.0001$, $\eta^2 = 0.97$) following the high-intensity exercise compared to pre-exercise (Table 2).

Lastly, there were no significant supplement x time interactions ($p > 0.05$) for peak power ($\eta^2 = 0.12$) (Figure 1), peak torque ($\eta^2 = 0.11$) (Figure 2), fatigue rate ($\eta^2 = 0.15$) (Figure 3), or lactate accumulation ($\eta^2 = 0.13$) (Figure 4).

**********INSERT TABLE 1 HERE

**********INSERT TABLE 2 HERE

**********INSERT FIGURE 1 HERE

**********INSERT FIGURE 2 HERE

**********INSERT FIGURE 3 HERE

**********INSERT FIGURE 4 HERE

DISCUSSION

There are few studies investigating CM, and to our knowledge, the current investigation was the first to compare the changes in quadriceps fatigue while supplementing with CM. The main findings from this investigation was that CM did not have an effect upon quadriceps fatigue within recreationally active males and females. Peak power, peak torque, fatigue rate, and lactate accumulation were no different with or without CM. It is apparent that these findings add to the already existing controversial findings of CM supplementation, thus, more research is still warranted. Although the different treatments had no effect upon lactate accumulation, the post-exercise values when pooled across treatments were statistically significant compared to the pre-exercise values. Additionally, considering that lactate was elevated post-exercise, we can assume that ammonia was elevated as well based upon the known relationship between lactate and ammonia (3).

Despite knowing that our protocol was efficient in raising metabolic by-products, we still were unable to report that CM had any impact in alleviating fatigue within the quadriceps muscles. Citrulline malate has been shown to be effective in performance, for supplementation has been reported to enhance skeletal muscle power output while promoting a greater oxidative energy turnover and a lower pH to power ratio (4). Furthermore, CM supplementation has been reported to improve muscle contractile efficiency in rats (8), prevent the decline in muscle force production in rats with endotoxemia (7), and facilitate ammonia clearance (18). Knowing that CM has been shown to enhance skeletal muscle power output, the protocol used within this investigation was chosen due to the likelihood of accumulating a high amount of metabolic by-products. However, peak power, peak torque, or fatigue rate were all unaltered with or without CM supplementation. Our results do compare with Cunniffe and colleagues who showed 12 g of

CM does not provide an acute ergogenic benefit (5). Within the Cunniffe article, participants performed 10 repeated maximal cycling sprints, with no changes observed in either peak power or mean power. On the other hand, others have shown that when supplementing with 8 g of CM, participants were able to increase work capacity by an average of 19% when performing high-intensity anaerobic exercise with short rest times (15). However, one potential discrepancy between the two conflicting articles was that in the Perez-Guisado article (15), a bench press protocol was used which incorporates smaller muscle mass, therefore, posing the argument that there is a different metabolic and cardiovascular demand between upper and lower body muscles. Nonetheless, our findings do agree with those of Cunniffe et al., which both protocols utilized exercises that had a major lower body component.

One of the primary promoted reasons for supplementing with CM is the ability to reduce the onset of fatigue through the elimination of metabolic by-product accumulation. Citrulline malate is supposedly able to reduce this waste accumulation via malate being able to act as a shuttle between the sarcoplasm and mitochondria, as of which would help to reduce lactate formation and increase pyruvate production (4, 21). Lactate is constantly being produced during both rest and exercise, however, during times of strenuous exercise, concentrations can be elevated to over 20 mmol$\cdot$L^{-1} (13, 14). Our study was effective in raising lactate levels throughout all treatments, however, there were no differences between the individual treatments. These results do follow those of Wax et al. (22) where there were no differences in lactate accumulations between CM and a placebo, despite lactate levels being elevated significantly following a lower-body resistance training protocol (22). Based upon our findings and those of Wax and colleagues (22), it is difficult to conclude that CM has an ergogenic benefit by acting as a buffer to help maintain an acid-base balance.

In light of L-citrulline being a precursor to NO production, it was our hypothesis that HR would have been lower with CM supplementation along with a greater amount of work being performed. However, no difference was found in both HR and total work with or without CM supplementation. Although our HR response with CM supplementation does agree with those of Wax et al. (22), the amount of reps completed was unaltered while Wax and colleagues were able to report a greater number of reps performed compared to a placebo (22). One major discrepancy between our work and that of Wax et al. (22) were the rest times. Within our investigation, participants rested only 30 sec between exercises, and one min between rounds. Within the Wax investigation, participants rested 3 min between all sets and exercises. Therefore, the longer rest periods may have been sufficient enough time for metabolic recovery. On the other hand, the shorter rest periods within our investigation may have been too short, thus, overwhelming the system with metabolic by-product formation. Our results do agree with others that found no change in work capacity (5), or those that found a decrease in performance while supplementing with CM (10). Those that did find CM supplementation to have a significant effect supplemented with 6 g/day for seven days, and found an enhanced endurance performance and a faster overall VO_2 kinetics (1). Therefore, chronic supplementation of CM may be the best way for it to have a positive effect with enhancing performance, as opposed to an acute consumption. Therefore, the limitation of the current investigation was the acute consumption of 8 g of CM, thus, future research should incorporate supplementing chronically with CM.

PRACTICAL APPLICATIONS

An acute dose (8 g) of CM provided to participants approximately 60 min before performing a high-intensity exercise session was ineffective in reducing fatigue or increasing the total amount of reps completed among recreationally trained individuals. Based upon our findings, we cannot support the use of CM to improve performance or help to lessen the onset of fatigue for body weight activates performed at a high-intensity. Practitioners interested in helping to increase performance or lessen fatigue should find alternative routes rather than supplementing with CM. Considering that CM is promoted to enhance skeletal muscle metabolism, future research should incorporate protocols that promote a high metabolic demand. This may include extending the time of work per set, such as going form 20 s of work per set to around 1-2 min of work per set. Additionally, future protocols should continue using exercises that incorporate multiple muscle groups with a short work:rest ratio to determine the effectiveness of CM on performance. This could provide beneficial information to those working in such arenas as tactical strength and conditioning.

ACKNOWLEDGMENS

No external funding was received to support the current investigation. The authors report no conflict of interest in relation to this work.

REFERENCES

1. Bailey SJ, Blackwell JR, Lord T, Vanhatalo A, Winyard PG, and Jones AM. l-Citrulline supplementation improves O2 uptake kinetics and high-intensity exercise performance in humans. J Appl Physiol (1985) 119: 385-395, 2015.
2. Bakeman R. Recommended effect size statistics for repeated measures designs. Behav Res Methods 37: 379-384, 2005.
3. Banister EWA, M.E.; Mekjavic, I.B.; Singh, A.K.; Legge, B.; Mutch, B.J.C. The time course of ammonia and lactate accumulation in blood during bicycle exercise. European Journal of Applied Physiology and Occupational Physiology 51: 195-202, 1983.
4. Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, and Cozzone PJ. Citrulline/malate promotes aerobic energy production in human exercising muscle. Br J Sports Med 36: 282-289, 2002.
5. Cunniffe B, Papageorgiou M, O'Brien B, Davies NA, Grimble GK, and Cardinale M. Acute Citrulline-Malate Supplementation and High-Intensity Cycling Performance. J Strength Cond Res 30: 2638-2647, 2016.
6. Cutrufello PT, Gadomski SJ, and Zavorsky GS. The effect of l-citrulline and watermelon juice supplementation on anaerobic and aerobic exercise performance. J Sports Sci 33: 1459-1466, 2015.
7. Giannesini B, Izquierdo M, Le Fur Y, Cozzone PJ, Verleye M, Le Guern ME, Gillardin JM, and Bendahan D. Beneficial effects of citrulline malate on skeletal muscle function in endotoxemic rat. Eur J Pharmacol 602: 143-147, 2009.
8. Giannesini B, Le Fur Y, Cozzone PJ, Verleye M, Le Guern ME, and Bendahan D. Citrulline malate supplementation increases muscle efficiency in rat skeletal muscle. Eur J Pharmacol 667: 100-104, 2011.
9. Hickner RC, Fisher JS, Ehsani AA, and Kohrt WM. Role of nitric oxide in skeletal muscle blood flow at rest and during dynamic exercise in humans. The American Journal of Physiology 273: H405-410, 1997.
10. Hickner RC, Tanner CJ, Evans CA, Clark PD, Haddock A, Fortune C, Geddis H, Waugh W, and McCammon M. L-citrulline reduces time to exhaustion and insulin response to a graded exercise test. Med Sci Sports Exerc 38: 660-666, 2006.
11. Jobgen WS, Fried SK, Fu WJ, Meininger CJ, and Wu G. Regulatory role for the arginine-nitric oxide pathway in metabolism of energy substrates. J Nutr Biochem 17: 571-588, 2006.
12. Jones AM, Wilkerson DP, and Campbell IT. Nitric oxide synthase inhibition with L-NAME reduces maximal oxygen uptake but not gas exchange threshold during incremental cycle exercise in man. J Physiol 560: 329-338, 2004.
13. Kilding AE and Jones AM. Validity of a single-visit protocol to estimate the maximum lactate steady state. Med Sci Sports Exerc 37: 1734-1740, 2005.
14. Kon M, Ikeda T, Homma T, Akimoto T, Suzuki Y, and Kawahara T. Effects of acute hypoxia on metabolic and hormonal responses to resistance exercise. Med Sci Sports Exerc 42: 1279-1285, 2010.
15. Perez-Guisado J and Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. J Strength Cond Res 24: 1215-1222, 2010.

16. Solomonson LP, Flam BR, Pendleton LC, Goodwin BL, and Eichler DC. The caveolar nitric oxide synthase/arginine regeneration system for NO production in endothelial cells. J Exp Biol 206: 2083-2087, 2003.
17. Sureda A, Cordova A, Ferrer MD, Perez G, Tur JA, and Pons A. L-citrulline-malate influence over branched chain amino acid utilization during exercise. Eur J Appl Physiol 110: 341-351, 2010.
18. Takeda K, Machida M, Kohara A, Omi N, and Takemasa T. Effects of citrulline supplementation on fatigue and exercise performance in mice. J Nutr Sci Vitaminol (Tokyo) 57: 246-250, 2011.
19. Vallance P, Collier J, and Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. Lancet 2: 997-1000, 1989.
20. Vanuxem PV, D.; Fomaris, E.; Bernasconi, P. The role of lactate and ammonium in fatigue. Gazette Medicale 7: 62-72, 1986.
21. Wagenmakers AJ. Muscle amino acid metabolism at rest and during exercise: role in human physiology and metabolism. Exerc Sport Sci Rev 26: 287-314, 1998.
22. Wax B, Kavazis AN, Weldon K, and Sperlak J. Effects of supplemental citrulline malate ingestion during repeated bouts of lower-body exercise in advanced weightlifters. J Strength Cond Res 29: 786-792, 2015.

Figure Legends

Figure 1. Supplement x Time Interaction for Peak Power.

Values are mean ± standard deviation; p = 0.24.

Figure 2. Supplement x Time Interaction for Peak Torque

Values are mean ± standard deviation; p = 0.28.

Figure 3. Supplement x Time Interaction for Fatigue Rate

Values are mean ± standard deviation; p = 0.18.

Figure 4. Supplement x Time Interaction for Lactate

Values are mean ± standard deviation; p = 0.25.

Table 1. Supplement main effects

Variable	Citrulline Malate (CM)	Placebo (PLA)	Control (CON)	p-value
Peak Power (W)	495 ± 162	493 ± 149	487 ± 132	0.82
Peak Torque (Nm)	159 ± 52	159 ± 48	156 ± 43	0.82
Fatigue Rate (%)	29 ± 5	28 ± 6	27 ± 7	0.60
Lactate ($mmol \cdot L^{-1}$)	7.02 ± 1.99	6.61 ± 1.42	7.19 ± 1.43	0.47
Final Heart Rate (bpm)	172 ± 11	175 ± 10	173 ± 8	0.30
Total Work (reps)	192 ± 29	189 ± 31	195 ± 27	0.35

Values are mean ± standard deviation.

Table 2. Time main effects

Variable	Pre-Exercise	Post-Exercise	p-value
Peak Power (W)	516 ± 152	467 ± 142	0.003*
Peak Torque (Nm)	166 ± 49	150 ± 45	0.003*
Fatigue Rate (%)	26 ± 4	31 ± 5	0.001*
Lactate ($mmol \cdot L^{-1}$)	1.97 ± 0.81	11.91 ± 2.18	0.001*

Values are mean ± standard deviation; *= $p < 0.05$.