

L-arginine α -ketoglutarate Does Not Increase Muscular Force Output or Endurance in Untrained or Resistance-Exercise Trained Young Females

Benjamin Wax, PhD

Andreas N. Kavazis, PhD

Heather E. Webb

Department of Kinesiology, Mississippi State University, Mississippi State, Mississippi 39762, USA

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ABSTRACT

Supplements marketed as nitric oxide stimulators have recently become extremely popular among people engaged in resistance exercise training, but their efficacy has not been fully documented. Thus, the aim of the current study was to investigate the ergogenic properties of acute L-arginine α -ketoglutarate ingestion in untrained and resistance exercise trained young females. Six untrained and 13 resistance-exercise trained young, healthy females ingested either 3,000 mg of L-arginine α -ketoglutarate or a placebo 45 minutes prior to a resistance exercise protocol in a randomized, double-blind crossover design. One repetition maximum on the chest press was obtained. Furthermore, total load volume (calculated as 60% of one repetition maximum X number of repetitions to failure) was determined. One week later, subjects ingested the other supplement, and the same

exercise protocol was performed. Our data showed significant differences ($p < 0.05$) between untrained and resistance-exercise trained subjects for both one repetition maximum and total load volume. However, one repetition maximum, and total load volume were no statistically significant different ($p > 0.05$) between subjects supplemented with L-arginine α -ketoglutarate or placebo for either untrained or resistance-exercise trained females. In addition, acute L-arginine α -ketoglutarate ingestion did not result in significant differences ($p < 0.05$) in heart rate or blood pressure before or after exercise. In conclusion, the results from our study indicate that acute ingestion of a nitric oxide stimulator provides no ergogenic benefit on maximal strength or muscular endurance in females as measured by the chest press exercise, regardless of the subject's training status.

INTRODUCTION

The use of supplements containing L-arginine to increase force output during

muscular exercise has recently become very popular among individuals engaged in resistance exercise training.^{1,2} Specifically, several supplements currently available in the market that contain L-arginine are often advertised as “nitric oxide stimulators.” The rationale of making these claims stems from the fact that nitric oxide can be endogenously synthesized from L-arginine via the enzyme nitric oxide synthase,^{1,3,4} and under certain circumstances, the concentration of L-arginine in the body can be the rate limiting step for nitric oxide production.⁴⁻⁶ An increased concentration of nitric oxide in the body following L-arginine supplementation could potentially improve blood flow due to vasodilation in the exercising skeletal muscles. Thus, the elevation in blood flow could theoretically improve exercise performance by increasing oxygen and nutrient delivery and/or waste-product removal from exercising skeletal muscles.⁷⁻⁹ Furthermore, it is common to find L-arginine supplements that are combined with α -ketoglutarate. Specifically, α -ketoglutarate is a metabolite produced by the oxidative decarboxylation of isocitrate. This is a process that occurs in the Krebs cycle.^{5,10} Thus, the inclusion of α -ketoglutarate in ergogenic supplements is based on the assumption that an increase in Krebs cycle flux is required to increase the rate of acetyl-CoA oxidation.¹¹ The increased Krebs cycle flux increases the amount of reducing equivalents (ie, nicotinamide adenine dinucleotide and flavin adenine dinucleotide) that can be used in the electron transport chain for adenosine triphosphate production.¹¹

Under physiological conditions, α -ketoglutarate can be replenished through the transamination of glutamate.¹² In this regard, glutamate is an amino acid necessary for protein anabolism, and it is known to be a very important excitatory nervous system neurotransmitter.^{13,14} Also, glutamate can be used for the synthesis of various amino acids by aminotransferases.¹⁵⁻¹⁷ As a result, supplementation with α -ketoglutarate may have a glutamate sparing effect, and thus may have both neurological and metabolic ergogenic

properties.

People that professionally or recreationally engage in resistance exercise activities use dietary sport supplements to increase exercise performance and the consumption of such supplements has exponentially increased in the past years.¹⁸⁻²⁰ One of these supplements commonly used today is L-arginine α -ketoglutarate. Therefore, the aim of this study was to investigate the potential ergogenic properties of an acute L-arginine α -ketoglutarate ingestion in both untrained and resistance-exercise trained young, female subjects. Further, we investigated the effects of an acute L-arginine α -ketoglutarate ingestion on systolic and diastolic blood pressure before and after resistance-exercise since this compound is marketed as a nitric oxide stimulator.

METHODS

Subjects

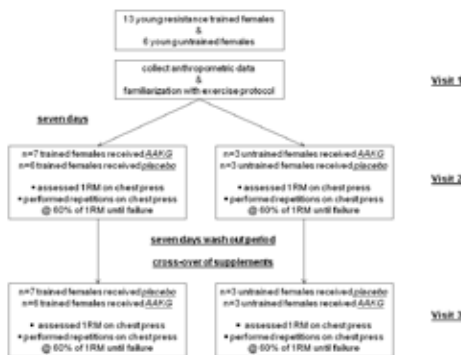
Nineteen apparently healthy females, six (21.2 ± 0.4 years, 1.64 ± 0.07 m, 62.2 ± 8.0 kg) who had not engaged in resistance exercise training for the previous 3 years and 13 (20.5 ± 1.0 years, 1.68 ± 0.06 m, 65.6 ± 13.0 kg) who had been engaged in resistance-exercise training continuously (at least three times per week) for the past 18 months volunteered for this investigation. Prior to the study, subjects completed a health history questionnaire and signed a statement of informed consent. All experimental procedures were reviewed and approved by the Institutional Review Board of Mississippi State University prior to the initiation of the study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Each subject reported to the laboratory three times (ie, visit 1, visit 2, and visit 3), and each visit was separated by 7 days. The first visit was used to determine subjects' anthropometric data and served as a familiarization session for the exercise protocol. During visit 1, subjects were instructed to refrain from strenuous exercise 48 hours before visit 2, and visit 3, and all subjects verified that have followed these guidelines.

Experimental Design

A randomized, counterbalanced, double-blind design was used for this study. Specifically, on visit 2, subjects ingested either L-arginine α -ketoglutarate or placebo, and then one repetition maximum and total load volume were obtained by using the chest press. Visit 3 occurred 7 days later, and subjects ingested the other supplement and performed the same experimental protocol. The supplementation dose and detailed exercise protocol used in this study are described below, and a summary of the study design is shown in Figure 1.

Figure 1. Illustration summarizing the experimental procedures and exercise protocol used in the study. AAKG = L-arginine α -ketoglutarate; 1RM = one repetition maximum.



Three thousand mg of over-the-counter L-arginine α -ketoglutarate (Healthwatchers DE Inc., Bohemia, NY, USA) or a placebo made of microcrystalline cellulose, croscarmellose sodium, magnesium stearate (Apotheca Company Inc., Woodbine, IA, USA) was ingested by subjects 45 minutes before the exercise protocol. The selected dose and timing of supplementation for this study were based on prior research.²¹

Exercise protocol

Forty-five minutes after ingestion of the supplement, subjects warmed up on an upright stationary bike (Life Fitness, Brunswick Corporation, Lake Fores, IL, USA) for 5 minutes. Then, subjects completed two warm-up sets of 10-12 repetitions on

the chest press (Cybex 4800, Cybex International, Inc., Medway, MA, USA) with a 5.7 to 11.3 kg mass based on each subject's strength.

In order to determine each subject's one repetition maximum (1RM), a trained technician determined a beginning resistance for the subject to perform their first 1RM trial. Then, 1RM was determined by increasing mass in 2.3- to 4.6- kg increments relative to the subject's ability to lift the first weight. The 1RM was obtained in three to six sets. The accepted 1RM was defined as the ability of the participant to complete a full repetition without assistance.

Following a 3-minute rest period, 60% of 1RM was placed on the chest press, and each subject completed as many repetitions as possible until failure occurred. Failure was defined as the inability to complete a full repetition without assistance. Total load volume (TLV) was calculated by multiplying the 60% of the 1RM mass by the number of repetitions to failure.

Heart Rate and Blood Pressure

Heart rate and blood pressure (systolic and diastolic) were recorded at rest and before the subjects ingested the supplement (PRE ingest), 45 minutes after the ingestion of the supplement, and before the exercise protocol (POST ingest), and within 2 minutes after failure has occurred (POST exercise) by using an automated instrument (SunTech Medical, Morrisville, NC, USA).

Statistical Analyses

All statistical analyses were performed by using the GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA). Data for one repetition maximum (1RM) and total load volume (TLV) between L-arginine α -ketoglutarate and placebo were analyzed by using a 2 (condition; L-arginine α -ketoglutarate, or placebo) x 2 (status; untrained or resistance trained) repeated measures analysis of variance. When the 2 x 2 repeated measures analysis of variance resulted in main effects significant difference, independent t-tests were run to determine significant differences between

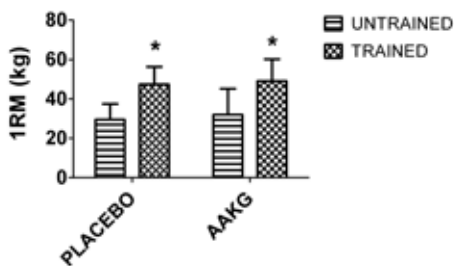
groups. Data for heart rate and blood pressure were analyzed by using a 2 (condition; L-arginine α -ketoglutarate or placebo) \times 3 (time; PRE ingest, POST ingest, and POST exercise) repeated measures analysis of variance. When the 2 \times 3 repeated measures analysis of variance resulted in main effects significant difference, paired t-tests were run to determine significant differences between groups. Statistical significance difference was established at $p < 0.05$. Data are reported as mean \pm standard deviation.

RESULTS

One Repetition Maximum (1RM)

Muscular force output was determined by obtaining the one repetition maximum (1RM) on the chest press. Our data shows that resistance exercise trained female subjects had statistically significantly higher ($p < 0.05$) 1RM than untrained subjects (Figure 2).

Figure 2. One repetition maximum (1RM) mass lifted. * indicates significant difference ($p < 0.05$) between untrained and trained subjects during same condition (placebo or L-arginine α -ketoglutarate (AAKG)). Data are as mean \pm standard deviation.

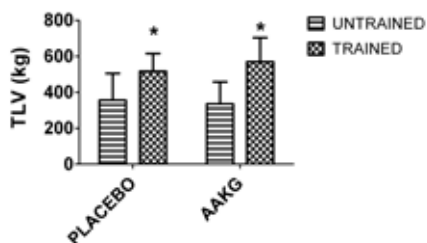


Total Load Volume (TLV)

Muscular endurance was determined by calculating total load volume (TLV) (ie, multiplying the number of repetitions performed to failure at 60% of 1RM). Similar to the results above, our data shows that resistance exercise trained female subjects had statistically significantly higher ($p < 0.05$) TLV than untrained subjects (Figure 3).

However, the results from our study did not show a statistical significant differ-

Figure 3. Muscular endurance was determined by calculating the total load volume (TLV = 60% of one repetition maximum mass lifted \times repetitions to failure). * indicates significant difference ($p < 0.05$) between untrained and trained subjects during same condition (placebo or L-arginine α -ketoglutarate (AAKG)). Data are as mean \pm standard deviation.



ence ($p > 0.05$) in 1RM or TLV between the L-arginine α -ketoglutarate and placebo treatments in either resistance exercise trained or untrained subjects (Figure 2 and Figure 3).

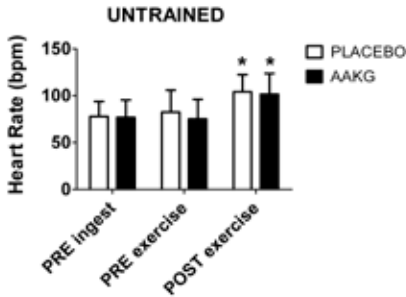
Heart Rate

Furthermore, heart rate was measured as an indicator of exercise intensity and to document that subjects exerted similar effort following L-arginine α -ketoglutarate and placebo supplementation.

In the untrained subjects, there were no statistical significant differences ($p > 0.05$) for heart rate after L-arginine α -ketoglutarate and placebo supplementation at either the PRE ingest or the POST ingest time periods (Figure 4). Following the exercise protocol, heart rate increased significantly ($p < 0.05$) after both L-arginine α -ketoglutarate and placebo supplementation compared to the PRE ingest and the POST ingest time periods (Figure 4). However, at the POST exercise time point, heart rate was not statistically significantly different ($p > 0.05$) between L-arginine α -ketoglutarate and placebo (Figure 4).

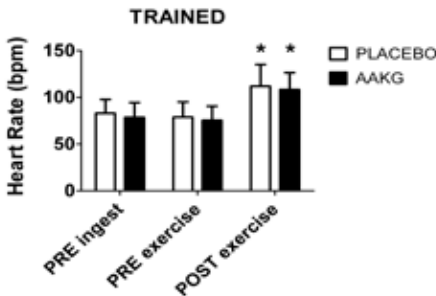
In regards to heart rate, similar results were obtained in resistance-exercise trained female subjects as in the untrained female subjects. Specifically, no statistical significant differences ($p > 0.05$) were detected between L-arginine α -ketoglutarate, and

Figure 4. Heart rate (beats per minute; bpm) in untrained female subjects at three time points (PRE ingest = before the subjects ingested the supplement, POST ingest = 45 minutes after the ingestion of the supplement and before the exercise protocol, POST exercise = within 2 minutes after failure has occurred). * indicates significant difference ($p < 0.05$) of POST exercise compared to PRE ingest and PRE exercise. AAKG = L-arginine α -ketoglutarate. Data are as mean \pm standard deviation.



placebo at either the PRE ingest or the POST ingest time periods (Figure 5). Heart rate increased significantly ($p < 0.05$) after resistance exercise, but it was not statistical-

Figure 5. Heart rate (beats per minute; bpm) in resistance trained female subjects at three time points (PRE ingest = before the subjects ingested the supplement, POST ingest = 45 minutes after the ingestion of the supplement and before the exercise protocol, POST exercise = within 2 minutes after failure has occurred). * indicates significant difference ($p < 0.05$) of POST exercise compared to PRE ingest and PRE exercise. AAKG = L-arginine α -ketoglutarate. Data are as mean \pm standard deviation.



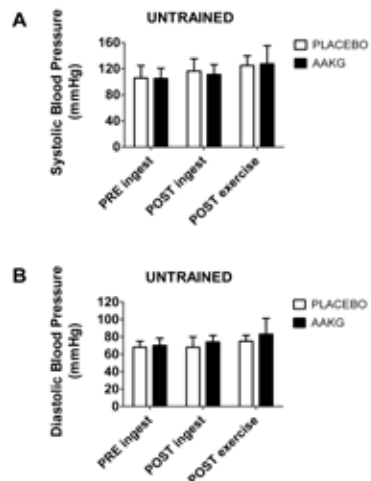
ly significantly different ($p > 0.05$) between L-arginine α -ketoglutarate and placebo (Figure 5).

Blood Pressure

Blood pressure was recorded in this study as L-arginine supplementation could have potentially resulted in elevated nitric oxide, and thus vasodilation. Nitric oxide induced vasodilation can decrease afterload, and thus could affect hemodynamics.

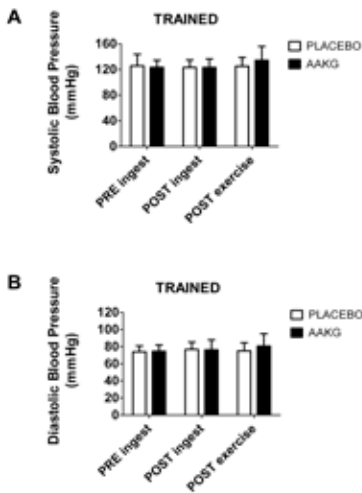
In untrained female subjects, we did not detect any statistical significant differences ($p > 0.05$) in either systolic blood pressure or diastolic blood pressure at rest and before the subjects ingested the supplement (PRE ingest), 45 minutes after the ingestion of the supplement, and before the exercise protocol (POST ingest), or within 2 minutes after failure has occurred (POST exercise) in either L-arginine α -ketoglutarate or placebo (Figure 6).

Figure 6. Panel A shows systolic blood pressure (mmHg) and panel B shows diastolic blood pressure in untrained female subjects at three time points (PRE ingest = before the subjects ingested the supplement, POST ingest = 45 minutes after the ingestion of the supplement and before the exercise protocol, POST exercise = within 2 minutes after failure has occurred). No significant differences ($p > 0.05$) were detected. AAKG = L-arginine α -ketoglutarate. Data are as mean \pm standard deviation.



Similar results for blood pressure (ie, no statistical significant differences ($p > 0.05$)) were obtained in resistance exercise trained female subjects (Figure 7).

Figure 7. Panel A shows systolic blood pressure (mmHg) and panel B shows diastolic blood pressure in resistance trained female subjects at three time points (PRE ingest = before the subjects ingested the supplement, POST ingest = 45 minutes after the ingestion of the supplement and before the exercise protocol, POST exercise = within 2 minutes after failure has occurred). No significant differences ($p > 0.05$) were detected. AAKG = L-arginine α -ketoglutarate. Data are as mean \pm standard deviation.



Supplements containing L-arginine (eg, L-arginine α -ketoglutarate) have become extremely popular in professional and recreational athletes who engage in resistance-exercise training. However, the efficacy and potential side effects of these supplements have not been fully determined. Thus, the aim of the current study was to investigate the ergogenic properties of acute L-arginine α -ketoglutarate ingestion in untrained and resistance trained young females.

Ergogenic supplements containing nitric oxide stimulators (eg, L-arginine α -ketoglutarate) are marketed to increase nitric oxide in the body and thus improve

athletic performance.⁷ Currently, research shows that L-arginine containing supplements can improve maximal strength,^{5,22} Wingate peak power,⁵ repeated sprint performance,²³ and fatigue resistance.^{23,24} However, Greer and Jones²⁵ did not find an ergogenic effect on exercise performance variables after consumption of an L-arginine containing supplement. These disparate results may be due to differences in exercise protocols, participant selection criteria, and/or dosage of the supplement.

The results from our study indicate that L-arginine α -ketoglutarate supplementation provided no ergogenic benefit during upper body muscular force output and endurance testing. Specifically, we measured one repetition maximum and total load volume by using the common chest press exercise. Moreover, we investigated whether resistance exercise trained and untrained females would respond differently after an acute ingestion of L-arginine α -ketoglutarate. Our results indicate that an acute dose of L-arginine α -ketoglutarate does not improve muscular force output or endurance in either resistance exercise trained or untrained females.

It is well known that heart rate increases linearly as exercise intensity increases.²⁶⁻²⁹ Thus, this physiological response of heart rate can be used as an indicator of exercise intensity.^{30,31} In the current study, resting heart rates were not different between subjects that ingested L-arginine α -ketoglutarate or placebo. This observation was the same regardless of the training status of the subjects. Heart rate significantly increased at the completion of the exercise protocol in subjects consuming either L-arginine α -ketoglutarate or placebo. However, no significant differences were found after L-arginine α -ketoglutarate or placebo ingestion indicating similar exertions under both conditions.

Supplementation with L-arginine α -ketoglutarate did not affect blood pressure either pre- or post-exercise. Importantly, a previous study showed that L-arginine

supplementation did not improve blood flow in subjects performing a resistance exercise protocol.³² In this regard, blood flow does increase after resistance exercise due to reactive hyperemia,³³ and this reaction can also be affected by various other factors.³⁴ For example, Tschakovsky et al.³⁵ reported that the nitric oxide pathway minimally affects the elevated muscle blood flow that occurs during exercise. Another study also reported that the nitric oxide pathway may not be the major factor in the observed increased blood flow after hand grip exercise.³⁶ Data also show that availability of L-arginine may not be the rate limiting aspect in the nitric oxide induced vasodilation^{37,38} since catecholamines and acetylcholine may also increase nitric oxide production and nitric oxide induced vasodilation during exercise.³⁹ As a result, supplementation with L-arginine before exercise may not result in further ergogenic properties.

In the past few years, the dietary supplement industry has blossomed to a multi-million dollar business and according to reports the use of dietary supplements by athletes varies from 45% to 88%.^{40,41} However, exogenous consumed dietary substances have the potential for adverse side effects. Currently the laws that govern dietary supplement sale are not strong, and thus rigorous studies of safety and efficacy of dietary supplements are lacking.⁴² This holds true for the supplement (ie, L-arginine α -ketoglutarate) used in this study, since it has been reported that L-arginine α -ketoglutarate containing supplements may be associated with adverse effects requiring hospital admission.⁴² For example, a male who ingested an L-arginine α -ketoglutarate supplement before working out developed palpitations, dizziness, vomited five times, and was witnessed to have a brief syncopal episode while working out.⁴² However, other investigators have reported that L-arginine α -ketoglutarate supplementation appeared to be safe and well tolerated.⁵

CONCLUSION

In conclusion, L-arginine containing supplements, such as L-arginine α -ketoglutarate,

are marketed as nitric oxide stimulators due to the role of nitric oxide in blood vessel vasodilatation. Acute L-arginine α -ketoglutarate supplementation provided no ergogenic benefit in this study, regardless of the subjects' training status. Based on the current literature, the use of L-arginine α -ketoglutarate is not recommended as an ergogenic aid for healthy individuals. Importantly, L-arginine α -ketoglutarate containing supplements may be associated with adverse effects requiring hospital admission.

CONFLICT OF INTEREST AND GRANT SUPPORT STATEMENTS

The authors declare that they have no conflict of interest.

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