

## CITRULLINE IN ELITE SPORTS: IS THERE A POINT?

E.N. Bezuglov<sup>1,2,3,4</sup>, B.A. Pirmakhanov<sup>5,6</sup>, O.B. Talibov<sup>3,4</sup>, K.V. Ivanov<sup>7</sup>, F.V. Takhavieva<sup>8</sup>,  
M.S. Butovsky<sup>7,8</sup>, A.V. Borisova<sup>7,8</sup>

<sup>1</sup>I.M. Sechenov First Moscow State Medical University, Moscow, Russia

<sup>2</sup>«Smart Recovery» Sports Medicine Clinic LLC, Moscow, Russia

<sup>3</sup>Sirius University of Science and Technology, Sochi, Russia

<sup>4</sup>High Performance Sport Laboratory, Moscow Witte University, Moscow, Russia

<sup>5</sup>Al-Farabi Kazakh National University, Almaty, Kazakhstan

<sup>6</sup>FC Kairat, Almaty, Kazakhstan

<sup>7</sup>FC Rubin, Kazan, Russia

<sup>8</sup>Kazan State Medical University, Kazan, Russia

### Abstract

Despite the contradictory data on the effect citrulline has on various aspects of physical performance and post-exercise recovery, it is commonly used in sports. Most of the available studies have been performed in recent years, which affirms the increased interest in this substance. The inconsistent data on the effectiveness of citrulline can be associated with the heterogeneity of both the research protocols and the study samples. Thus, coaches and athletes of various levels may be interested in the results of high methodological quality research that assessed the effect of acute and chronic intake of citrulline on various aspects of physical performance.

The research purpose is to evaluate the effect of citrulline on physical performance in elite athletes.

Materials and methods. The Pubmed database was searched for randomized controlled trials in English conducted from 2000 to 2021 among healthy subjects of different levels of physical fitness to assess the effect of a single standardized intake of citrulline or citrulline malate on various parameters of physical performance and post-exercise recovery, such as rating of perceived exertion, delayed onset muscle soreness, lactate, creatine kinase, strength, power, endurance, speed, heart rate and blood pressure.

The words 'citrulline malate' and 'citrulline', as well as their combinations with words and phrases 'rating of perceived exertion', 'delayed onset muscle soreness', 'lactate', 'strength', 'power', 'endurance', 'speed', 'physical performance', 'heart rate', 'creatine phosphokinase' and 'blood pressure' were used as search queries.

The search was carried out by two independent experts where any disputes were resolved by the opinion of the main author of the study. The exclusion criteria were as follows:

- age of participants less than 18 years;
- participants with any somatic pathology;
- use of citrulline or citrulline malate in combination with other substances.

Results. A total of 1286 studies were found, of which 22 (427 participants) were randomized controlled trials that met the inclusion criteria. The majority of research was conducted on amateur-level athletes or physically active healthy people from the general population aged 18 to 51 years. Six studies analyzed the effect of a course standardized ingestion, while 16 analyzed the effect of a single dose of citrulline on various aspects of physical performance, cardiovascular performance and post-exercise recovery.

When analyzing the data on the effectiveness of citrulline, it was reported that 10 out of 22 studies could provide no evidence that citrulline effectively improved any of the analyzed parameters. In other studies, citrulline was most effective in improving strength parameters (6 studies), endurance parameters (5 studies) and reducing the severity of delayed onset muscle soreness (4 studies). Regarding the rating of perceived exertion, only 3 studies reported a positive effect of citrulline. Two more studies provided evidence of a negative effect on the rating of perceived exertion. There was also no evidence to suggest the effectiveness of citrulline on creatine phosphokinase concentration. The effectiveness of citrulline in reducing the severity of delayed onset muscle soreness at any time after exercising was shown in only 2 studies.

Conclusion. The use of citrulline is not recommended for elite athletes. The data obtained during the analysis of studies on the effect of citrulline on various aspects of physical performance were contradictory. Only a small

number of studies examined data on the effectiveness of citrulline in improving performance indicators that are important for athletes, such as strength, endurance, delayed onset muscle soreness and lactate concentration. In addition, there is a possibility of unintentional violation of anti-doping rules.

**Keywords:** citrulline, performance, post-exercise recovery, elite sports.

## ЦИТРУЛЛИН В ЭЛИТНОМ СПОРТЕ: ЕСТЬ ЛИ В ЭТОМ СМЫСЛ?

Э.Н. Безуглов<sup>1,2,3,4</sup>, e-mail: e.n.bezuglov@gmail.com, ORCID: 0000-0003-3828-0506

Б.А. Пирмаханов<sup>5,6</sup>, e-mail: pirmakhanov.b@gmail.com, ORCID: 0000-0002-1512-8141

О.Б. Талибов<sup>3,4</sup>, e-mail: oleg.talibov@gmail.com, ORCID: 0000-0001-6381-2450

К.В. Иванов<sup>7</sup>, e-mail: kirill-ivanov@yandex.ru, ORCID: 0000-0003-2836-4343

Ф.В. Тахавиева<sup>8</sup>, e-mail: fartah@list.ru, ORCID: 0000-0002-7387-8944

М.С. Бутовский<sup>7,8</sup>, e-mail: dr mike81@inbox.ru, ORCID: 0000-0003-1295-9457

А.В. Борисова<sup>7,8</sup>, e-mail: doc.borisova@bk.ru, ORCID: 0000-0002-6786-0510

<sup>1</sup>Первый Московский государственный медицинский университет им. И.М. Сеченова, Москва, Россия

<sup>2</sup>ООО «Клиника спортивной медицины» «Смарт Рекавери», Москва, Россия

<sup>3</sup>Научно-технический университет «Сириус», Сочи, Россия

<sup>4</sup>Лаборатория спорта высших достижений, Московский университет имени Витте, Москва, Россия

<sup>5</sup>Казахский национальный университет им. Аль-Фараби, Алматы, Казахстан

<sup>6</sup>ФК «Кайрат», Алматы, Казахстан

<sup>7</sup>ФК «Рубин», Казань, Россия

<sup>8</sup>Казанский государственный медицинский университет, Казань, Россия

### Актуальность

Несмотря на противоречивые данные о влиянии цитруллина на различные аспекты физической работоспособности и восстановления после тренировки, он широко используется в спорте. Большинство доступных исследований было проведено в последние годы, что подтверждает возросший интерес к этому веществу. Противоречивые данные об эффективности цитруллина могут быть связаны с неоднородностью как протоколов исследований, так и исследуемых образцов. Таким образом, тренеров и спортсменов различного уровня могут заинтересовать результаты высококачественных методологических исследований, в которых оценивалось влияние однократного и длительного приема цитруллина на различные аспекты физической работоспособности.

**Цель.** Целью данного систематического обзора явилась оценка влияния цитруллина на физическую работоспособность элитных спортсменов.

**Материалы и организация исследования.** В базе данных Pubmed был проведен поиск рандомизированных контролируемых исследований на английском языке, проведенных с 2000 по 2021 годы среди здоровых людей с различным уровнем физической подготовленности для оценки влияния однократного стандартизированного приема цитруллина или цитруллина малата на различные параметры физической работоспособности и восстановления после тренировки, такие как оценка воспринимаемой нагрузки, мышечная болезненность с отсроченным началом, уровни лактата и креатинкиназы, сила, мощность, выносливость, скорость, частота сердечных сокращений и артериальное давление.

Слова «цитруллин малат» и «цитруллин», а также их сочетания со словами и фразами «оценка воспринимаемой нагрузки», «мышечная болезненность с отсроченным началом», «лактат», «сила», «мощность», «выносливость», «скорость», «физическая работоспособность», «частота сердечных сокращений», «креатинфосфокиназа» и «артериальное давление» использовались в качестве поисковых запросов.

Поиск проводился двумя независимыми экспертами, где любые споры разрешались мнением основного автора исследования. Критерии исключения были следующими:

- возраст участников менее 18 лет;
- участники с любой соматической патологией;
- использование цитруллина или цитруллина малата в сочетании с другими веществами.

**Результаты.** Всего было обнаружено 1286 исследований, из которых 22 (427 участников) были рандомизированными контролируемыми исследованиями, которые соответствовали критериям включения.

Большинство исследований проводилось на спортсменах любительского уровня или физически активных здоровых людях в возрасте от 18 до 51 года. В шести исследованиях анализировался эффект курсового приема внутрь, в 16 – влияние однократной дозы цитруллина на различные аспекты физической работоспособности, показатели сердечно-сосудистой системы и постнагрузочного восстановления.

По итогам анализа данных об эффективности цитруллина было показано, что 10 из 22 исследований не смогли предоставить никаких доказательств того, что цитруллин эффективно улучшал какой-либо из изучаемых параметров. В других исследованиях цитруллин был наиболее эффективен в улучшении силовых параметров (6 исследований), параметров выносливости (5 исследований) и снижении выраженности отсроченной мышечной болезненности (4 исследования). Что касается оценки воспринимаемой нагрузки, то лишь в 3 исследованиях сообщалось о положительном эффекте приема цитруллина. Еще два исследования предоставили доказательства негативного влияния на оценку воспринимаемой нагрузки. Также не было никаких доказательств, свидетельствующих об эффективности цитруллина в отношении концентрации креатинфосфокиназы. Эффективность цитруллина в снижении тяжести мышечной болезненности с отсроченным началом в любое время после тренировки была показана только в 2 исследованиях.

**Заключение.** Имеющиеся в настоящее время данные не позволяют рекомендовать применение цитруллина элитными спортсменами. Данные, полученные в ходе анализа исследований о влиянии цитруллина на различные аспекты физической работоспособности, были противоречивыми. Лишь в небольшом количестве исследований изучались данные об эффективности цитруллина в улучшении важных для спортсменов показателей работоспособности, таких как «сила», «выносливость», «болезненность мышц с отсроченным началом» и «концентрация лактата». Кроме того, существует вероятность непреднамеренного нарушения антидопинговых правил.

**Ключевые слова:** цитруллин, работоспособность, восстановление после тренировки, элитный спорт.

## INTRODUCTION

Despite the contradictory data on the effect citrulline has on various aspects of physical performance and post-exercise recovery, it is commonly used in sports. Most of the available studies have been performed in recent years, which affirms the increased interest in this substance. The inconsistent data on the effectiveness of citrulline can be associated with the heterogeneity of both the research protocols and the study samples. Thus, coaches and athletes of various levels may be interested in the results of high methodological quality research that assessed the effect of acute and chronic intake of citrulline on various aspects of physical performance.

This review included 22 randomized placebo-controlled trials analyzing 427 members of the general population of both sexes, aged 18 to 51 years. The body of research available has examined physically active healthy members of the general population and recreational athletes opposed to elite athletes. Strength and aerobic performance were estimated, along with indicators such as heart rate (HR), rating of perceived exertion (RPE), delayed onset

muscle soreness (DOMS) and lactate concentration (La). The analysis provided contradictory results on the effect of citrulline on various aspects of physical performance and post-exercise recovery, and the scant research conducted among elite athletes was notably.

Concurrently, the available literature regarding the effectiveness of citrulline was gathered from the general population who performed non-specific exercises, therefore this data cannot be extrapolated to elite sports. Considering these factors, the current environment does not allow the recommendation of citrulline use by elite athletes.

Over the last decade, there has been an increasing interest in assessing the effectiveness of citrulline when aiming to improve various aspects of athletic performance.

Although, there is no published literature on the effectiveness of citrulline among elite athletes, which prevents any clear conclusion being established regarding its application in elite sports.

The analysis of training protocols, dosing regimens and sampling of participants in research of high methodological quality that assess the effect

of citrulline on various aspects of performance and post-exercise recovery does not advocate its usage in elite athletes.

Citrulline is an essential amino acid found in the body under natural conditions. Citrulline is an endogenous precursor of arginine, which is the main substrate for nitric oxide synthase (NO-synthase, NOS) in the NOS pathway. Arginine affects various body functions by regulating vasodilation, blood flow, mitochondrial respiration, and platelet function [14, 26].

Arginine is used as a supplement with a proven vasodilatory effect, where one of the main mechanisms behind its potential performance-enhancing effect is the increase in blood flow to the skeletal muscle due to endothelium-dependent vasodilation [22].

The potential performance improvement produced by citrulline is also mediated by several other mechanisms, namely; 1) an enhanced ammonia and lactic acid metabolism and improved oxygen delivery caused by increased vasodilation [5]; 2) a significant increase in the rate of oxidative phosphorylation during exercise (+34%), and in the rate of post-exercise phosphocreatine recovery (+20%) [2]; 3) an increase in the plasma concentration of L-arginine and enhanced NO-dependent signaling during intense exercise, which can disrupt metabolic homeostasis and lead to amino acid catabolism and limited availability of L-arginine; 4) ensuring the delivery of nitrogen which is required to maintain sufficient nitrogen balance and as a precursor of arginine, which is synthesized in the kidneys, endothelial and immune cells [1]; and 5) the conversion of citrulline into arginine is considered the rate-limiting step of the NOS pathway, and adding citrulline increases the arginine plasma concentration [17, 18].

Unlike arginine, citrulline is not used by the gut and is not absorbed by the liver. It is most effectively absorbed when administered perorally, and is then transported to the kidneys where it is converted into L-arginine [30]. Simultaneously, the research confirming that citrulline improves vasodilation and skeletal muscle perfusion is scant and contradictory. However, several studies have

reported that L-citrulline supplements may improve physical performance and recovery [8].

In sports, citrulline malate (CM) is often used as a performance-enhancing supplement. Citrulline malate is an organic salt of citrulline that consists of the essential amino acid L-citrulline and L-malic acid (an intermediate substance in the citric acid cycle).

According to Jagim et al., CM is present in more than 70% of the most popular multi-substance pre-workout supplements. In this regard, it is secondary only to beta-alanine (87%) and caffeine (86%), and is combined significantly more often than tyrosine, taurine and creatine (63%, 51% and 49%, respectively). Furthermore, the average dose of CM in these supplements is  $4.0 \pm 2.5$ g [11].

Citrulline is not included on the prohibited list of the World Anti-Doping Agency. However, its use, including as part of a combined pre-workout supplement, may enhance the risk of an unintentional violation of anti-doping regulations due to the widespread contamination of various legal dietary supplements and sports nutrition aids with prohibited substances [15].

According to unpublished data obtained by the authors of this article when conducting an anonymous survey of elite Russian endurance athletes, more than 40% of these athletes used citrulline and considered it effective during recovery (own unpublished data). Thus, citrulline is among the most commonly used substances in athletes of varying competitive levels, despite the fact that there is still no scientifically proven evidence to suggest that, as well as a number of other substances (branched chain amino acids, adenosine triphosphate,  $\beta$ -hydroxy- $\beta$ -methylbutyrate, minerals, most vitamins and arginine), are indeed effective [29].

What are the potential positive effects of citrulline that cause its active use by professional athletes? According to currently available scientific literature, the range of applications of citrulline is vast. There is evidence to suggest its effectiveness in the treatment of asthenic syndromes and erectile dysfunction, sarcopenia in elderly, pulmonary hypertension in newborns, carbamoyl phosphate



synthetase deficiency and ornithine transcarbamylase deficiency. It has also been shown to effectively lower blood pressure in hypertension patients, as well as an increase in strength and aerobic performance and enhance post-exercise recovery [14, 2, 1, 25, 19, 4, 9, 23, 7, 3, 24, 12, 6]. Therefore, a real-world assessment into the effectiveness of citrulline and the implementation of proven protocols for its usage that consider the specifics of the sporting discipline and the daily training process of professional athletes is of great practical interest.

Thus, the purpose of this study was to analyze the results of existing research of high methodological quality which assessed the standardized and single isolated ingestion of citrulline on various parameters of physical performance and post-exercise recovery.

The systematic review of the literature aimed to investigate whether there is the effect of citrulline on the physical performance in elite athletes.

## MATERIALS AND METHODS

The Pubmed database was searched for randomized controlled trials in English conducted from 2000 to 2021 in healthy subjects of different levels of physical fitness to assess the effect of a single standardized intake of citrulline or citrulline malate on the following parameters of physical performance and post-exercise recovery: rating of perceived exertion (RPE), the severity of delayed onset muscle soreness (DOMS), concentrations of lactate (La), creatine phosphokinase (CK), strength, power, endurance, speed, heart rate (HR) and blood pressure.

The words 'citrulline malate' and 'citrulline', as well as their combinations with words and phrases 'rating of perceived exertion', 'delayed onset muscle soreness', 'lactate', 'strength', 'power', 'endurance', 'speed', 'physical performance', 'heart rate', 'creatine phosphokinase' and 'blood pressure' were used as search queries.

The term «elite athletes» referred to athletes who had consistently performed in their chosen sport for at least two years and had competed in adult national championships (for individual sports) or

had played for teams of the highest division in the championship of their country.

To ensure a thorough search of publications met the acceptance criteria, the references and recommended articles of each of the forementioned studies were also analyzed.

The search was carried out by two independent experts where any disputes were resolved by the opinion of the main author of the study. The exclusion criteria were as follows:

- age of participants less than 18 years;
- participants with any somatic pathology;
- use of citrulline or citrulline malate in combination with other substances.

Since all the collated data were in the public domain, local ethics committee approval was not required.

## RESULTS

A total of 1286 studies were found, of which 22 (427 participants) were randomized controlled trials (RCT) that met the inclusion criteria. The majority of research was conducted in amateur-level athletes or physically active healthy people from the general population aged 18 to 51 years. Six studies analyzed the effect of a standardized ingestion, while 16 analyzed the effect of a single dose of citrulline on various aspects of physical performance, cardiovascular performance and post-exercise recovery. Commonly, RPE, La, DOMS, dynamic changes in strength and aerobic performance and HR were estimated.

In studies that examined the effect of various citrulline protocols, the standardized dose was 2.4-6g daily for 1-4 weeks. Only 1 study analyzed the effect of a citrulline protocol on the concentration of La in Turkish handball players from 1Lig. (1g 3 times a day for 4 weeks), but these players could not be considered elite athletes. While 2 studies analyzed the effects of citrulline in team sports, the participants were the aforementioned handball players of the Turkish 1Lig and members of varsity basketball and football teams [20], [21]. When the effect of a single dose of citrulline was analyzed, doses of 1.17 to 12g were administered 40-120 minutes before exercise. Most often, 6-8 g of citrulline were used in single-dose experiments.

**Table 1 – Protocols for the implementation of citrulline malate and citrulline used in research of high methodological quality conducted in physically healthy adults' representative of the general population and athletes.**

**Note:** «-» corresponds to a negative effect on the studied parameter; «+» corresponds to a positive effect on the studied parameter; «0» corresponds to a neutral effect on the studied parameter

Authors	Design	Participants	Dosing	Analyzed parameters	Participant level	Effective-ness	Adverse effects
1. Cunniffe B, 2016	RDB	10 well-trained men	12 gofCM, <b>single dose</b> , 60 minutes before a repeated cycling sprint	HR (-), time to exhaustion (0), power (0), RPE (0)	Amateurs		No
2. Farney TM, 2019	RSB randomized single-blind	12 healthy participants (6 men, 6 women), mean age 24.1±3.9 years	8 gofCM, <b>single dose</b> , before a high-intensity strength workout	Isokinetic leg extension pre- and post-exercise (peak power, maximum torque) (0), RPE (0), La (0)	Amateurs		N/A (not assessed)
3. Gonzalez AM, 2018	RDB	12 amateur men	8 gofCM, <b>single dose</b> , 40 minutes before a high-intensity strength workout	Strength endurance (0), exercise effectiveness (0), fatigue (0), RPE (0)	Amateurs		N/A
4. Wax B, 2016	RDB	14 well-trained men, mean age 23.3±1.5 years, mean height 1.79±0.07 m, mean weight 87.8±9.1 kg	8 gofCM, <b>single dose</b> , 60 minutes before a high-intensity strength workout	Strength endurance (+), blood La (0), arterial blood pressure (0)	Amateurs		N/A
5. Glenn JM, 2017	RDB	15 women, mean-age 23±3 years, mean height 162.6 cm, mean weight 67.1 kg	8 gofCM, <b>single dose</b> , 60 minutes before a high-intensity strength workout	Strength endurance (+), HR (0) and RPE (+)	Amateurs		No
6. Glenn JM, 2016	RDB	17 women (51±9 years), tennis players	8 gofCM, <b>single dose</b> , 60 minutes before testing	Strength (+), power (0), anaerobic endurance (+)	Amateurs		No
7. Gills JL, Glenn 2021	RDB	28 young men (20.9±2.8 years), amateur cyclists	8 gofCM, <b>single dose</b> , 60 minutes before testing	Aerobic endurance (0), anaerobic endurance (0)	Amateurs		N/A
8. Stanelle ST, 2020	RDB	9 well-trained men (24±3 years), cyclists	7 days <b>regimen</b> of 6 g CM daily (last dose taken 120 minutes before the test, a 40-km cycle with a following repeated sprint)	Aerobic endurance (+) HR (-), RPE (+), mean power output during exercise (+)	Amateurs		N/A
9. Suzuki T, 2016	RDB	22 well-trained men	A 7-day <b>regimen</b> of 2,4 gL-citrulline daily, 2,4 gofL-citrulline administered on the 8 <sup>th</sup> day 60 minutes before a 60-minute exercise cycle ride	Endurance (+), RPE (+)	Amateurs		N/A
10. Chappell AJ, 2020	RDB	19 participants (8 women), mean age 25.7±7.7 years	8 gofCM, <b>single dose</b> before a strength workout	Number of reps (0), La level (0), creatine phosphokinase level (0), DOMS (+)	Amateurs		No
11. Martínez-Sánchez A, 2017	RDB	21 healthy men, mean age 35.3±11.4 years, mean height 175.5±7.6 cm, mean age 73.6±9.1 kg	Fashion watermelon juice enriched with CM (3.45 g per 500 ml), <b>single dose</b> 120 minutes before a half-marathon	Jump height (+), HR and RPE (0), La concentration (+), DOMS (+)	Amateurs		N/A
12. Hwang P, 2018	RDB	75 men	8 weeks of strength training; a <b>regimen</b> of 2 g daily 1 h before the workout	Strength endurance (0), muscle mass and strength after 8 weeks (0)	Amateurs		No

13. Bailey SJ, 2015	RDB	10 healthy men	A 7-day <b>regimen</b> of 6 g of CM daily	Kinetics of lung oxygen consumption (Vo2)(+), physical performance(+), blood pressure(+)	Amateurs		N/A
14. da Silva D.K., 2017	RDB	9 young untrained men, mean age 24.0±3.3 years	6 gofCM, <b>single dose</b> , before a high-intensity strength workout	Strength endurance (0), DOMS and RPE (0), CK level and testosterone/ cortisol ratio (0)	Amateurs		No
15. Chappell AJ, 2018	RDB	18 physically healthy men and women (13 men, 5 women), mean age 23.67±2.41 years, mean weight 75.15±13.67 kg	8 gofCM, <b>single dose</b> , before a high-intensity strength workout	Strength endurance (0), post-workout isometric, concentric and eccentric peak force (0), DOMS(-)	Amateurs		No
16. Pérez-Guisado J, 2010	RDB	41 men	8 gofCM, <b>single dose</b> , before a high-intensity strength workout (bench press, 16 sets)	DOMS(+), strength endurance(+)	Amateurs		<b>Stomach discomfort (14.63% of the participants)</b>
17. Wax B, 2015 Mar	RDB	12 men	8 gofCM, <b>single dose</b> , before a high-intensity strength workout	Strength endurance (+), level (0), HR (0) and blood pressure before and after the exercise (0)	Amateurs		No
18. Tarazona-Díaz MP, 2013	RSB	7 athletes Students of the Department of Physical Activity and Sport Science, Faculty of Sport, Catholic University of Murcia (7 men, mean age±SD 22.7±0.8 years; mean weight 68.9±3.8 kg; mean height 170.8±3.6 cm; mean BMI 24.0±0.6 kg/m <sup>2</sup> ). The subjects were not competitive athletes, but did sports regularly.	500 ml of organic watermelon juice (1.17 gofL-citrulline), enriched watermelon juice (4.83 g of L-citrulline + 1.17 g of watermelon), <b>single dose</b> , before a 1RM load on a cycle ergometer	HR (+) and DOMS(+)	Amateurs		N/A
19. Kiyici, 2017	RSB	22 handball players during pre-season training (11 athletes, mean age 21.57±4.58 years, mean height 179.86±5.73 cm, mean weight 70.59±7.08 kg) received Stimol; 11 handball players, mean age 18.00±2.00 years, mean weight 179.27±10.55 kg, mean weight 79.35±7.08 kg received placebo	A 1-month <b>regimen</b> of 1 g of CM (Stimol), thrice daily	Lactate immediately after the exercise (+), but not before it or 5 and 20 minutes after it	Professionals (Turkish Handball 1.Lig)		N/A
20. Bailey, 2016	RDB	8 men	A 16-day <b>regimen</b> of 3.4 g of CM daily	Blood pressure (-), time to exhaustion (0)	Amateurs		No
21. Cutrufello PT, 2015	RDB	22 physically active men and women (11 participants of each sex)	1 and 6 gof citrulline, <b>single dose</b> , 60 and 120 minutes before the workout	Bench press (0), time to exhaustion in a treadmill test (0), maximal oxygen consumption (0)	Amateurs		No
22. Hickner RC, 2006	RDB	17 young physically active healthy men and women of 18-34 years	<b>Single dose</b> , 3 g 3 h before test, or 9 g over 24 h prior to testing	Time to exhaustion (-), RPE (-), maximal oxygen consumption (0)	Amateurs		N/A

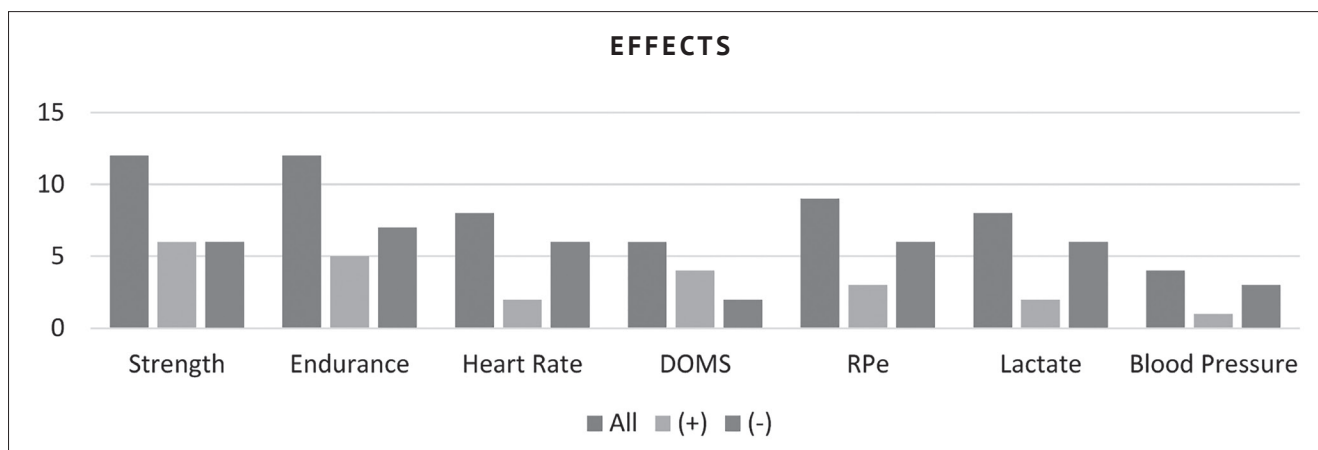


Figure – The number of RCTs analyzing the effect of citrulline on the parameters of physical performance and post-exercise recovery

Table 2 – The number and results of RCTs that evaluated the effect of single standardized intake of citrulline on physical performance and post-exercise recovery

Effects	Total	(+)	(-)	References (+) (#)
Strength	12	6	6	4,5,6,8,11,18
Endurance	12	5	7	6,8,9,13,16
Heart Rate(HR)	8	2	6	8,18
DOMS	6	4	2	10,11,16,18
RPE	9	3	6	5,8,9
Lactate (La)	8	2	6	11,19
Blood Pressure	4	1	3	13

When data on the effectiveness of citrulline obtained from the selected studies were analyzed, it was reported that 10 out of 22 studies could provide no evidence that citrulline effectively improved any of the analyzed parameters. In other studies, citrulline was most effective in improving strength parameters (6 studies), endurance parameters (5 studies) and reducing the severity of DOMS (4 studies). Regarding RPE, only 3 studies reported a positive effect of citrulline. Two more studies provided evidence of a negative effect on RPE. There was also no evidence to suggest the effectiveness of citrulline on CK concentration. The level of this enzyme is often used as an indicator of the severity of physical activity and muscle damage [Brancaccio et al.]. The effectiveness of citrulline in reducing La production at any time post-exercise was shown in only 2 studies.

Notably, administering 1-12g of citrulline can be deemed safe from the development of adverse effects, as only 1 out of 10 studies analyzed reported any negative effects. Contrastingly, Pérez-Guisado

et al. found that 15% of participants developed stomach discomfort [20].

Currently, there is growing interest in the benefits of citrulline and the potential positive affect on various aspects of physical performance. The majority of available research concerning high methodological quality performed in adult populations have been published in the last 10 years. Recent meta-analyses have shown that the administration of a single large dose of CM may have a positive effect of varying intensity on DOMS and RPE, but not on blood La levels [21], [27].

Concurrently, there is also evidence that citrulline is more effective than arginine in improving physical performance as an ergogenic aid. According to a meta-analysis conducted by Huerta Ojeda et al., citrulline had a positive effect on RPE and muscle pain in addition to a decrease in La concentrations. Although, there is still a lack of empirical evidence concerning the effective dosage and timing of dose of citrulline when employed to positively affect physical performance [10].



When examining randomized controlled trials, 50% of this research could not find evidence of its effectiveness for improving the various aspects of performance. In all studies, citrulline was only ingested before exercise, and not during or after it. It should also be noted that more than 90% of studies were conducted with amateur athletes and physically active representatives of the general population, which does not allow extrapolation of the data to high-level athletes.

This notion was confirmed by Lamprecht., who highlighted that the effectiveness of administering nitric oxide donors (which included citrulline) depended on the individuals current training status. Studies examining untrained and physically healthy subjects have shown that nitric oxide donors can improve the tolerance of aerobic and anaerobic exercises, but no positive effect on performance was observed in studies involving highly trained athletes [13].

Sureda et al., supported the findings of Lamprecht., suggesting that the effect of citrulline on physical performance depends on the existing fitness level of the subject, and additionally citrulline did not produce a positive effect in well-trained representatives of the general population [26]. It is also important to recognize that the type of physical activity employed in these studies (leg press, bench press, pull-ups, cycle ergometry) are not specific to all sporting populations.

Furthermore, high-level athletes often use several dietary supplements and medicinal substances during a training week (according to Maughan et al., 85% of elite track and field athletes are currently consuming such aids). Commonly used supplements include vitamins, minerals, protein, creatine, and various 'ergogenic' compounds [16]. In the Maughan et al. study cohort, the mean supplement and medicinal substance count for each of the athletes were 1.7 and 0.8, respectively. The most commonly used substances were non-steroidal anti-inflammatory drugs (0.27 per athlete), respiratory tract medication (0.21 per athlete) and analgesics (0.13 per athlete) [28].

Undoubtedly, the combined ingestion of various ergogenic supplements and medicinal products such as NSAIDs can significantly affect important

parameters of exercise tolerance and fatigue such as RPE and DOMS and thus make it impractical to objectively assess the individual effect of each substance. These findings suggest that the available data are extreme heterogeneous in terms of training protocols, participant sampling, dose sizes and dosing regimens.

Future research should consider the effectiveness of citrulline usage in professional athletes. These studies should analyze various protocols and use sport-specific exercises of sub-maximal and maximal intensity to determine the real-world impact of citrulline implementation in the training and competition activities of professional athletes.

## CONCLUSION

The analysis of the existing randomized controlled trials into the effect of citrulline on various aspects of physical performance and post-exercise recovery showed an extreme heterogeneity of design and an inconsistency in the obtained data.

This research did not involve elite athletes or use strength specific exercises relevant to all sports. Furthermore, only a small number of studies examined data on the effectiveness of citrulline in improving performance indicators important for athletes, such as strength, endurance, DOMS and La concentration.

It is also noteworthy that citrulline is included in many combined pre-workout supplements. This can lead to an un-intentional violation of anti-doping regulations caused by contamination of these supplements with prohibited substances not clearly indicated.

Given these important factors, the current sporting context does not support the recommendation of citrulline usage by elite athletes. Future studies need to assess the effectiveness of CM administered to professional athletes using real-world dosing protocols and sport-specific exercises.

**Disclosure of interest:** Author **Bezuglov Eduard** is employed by «Smart Recovery» Sports Medicine Clinic LLC, Moscow, Russian Federation. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## REFERENCES

1. Bahri S., Zerrouk N., Aussel C., Moinard C., Crenn P., Curis E., Chaumeil J.C., Cynober L., Sfar S. Citrulline: from metabolism to therapeutic use. *Nutrition*. 2013 Mar; 29(3):479-84.
2. Bendahan D, Mattei JP, Ghattas B, Confort-Gouny S, Le Guern ME, Cozzone PJ. *Br J Sports Med*. 2002 Aug;36(4):282-289. DOI: 10.1136/bjsm.36.4.282.
3. Casonatto J., Cavalari J.V., Goessler K.F., Christofaro D.G.D., Polito M.D., Enokida D.M., Grandolfi K. Citrulline malate supplementation might potentiate post-exercise hypotension in hypertensives: A 24-hour analysis. *Science & Sports*, Volume 34, Issue 4, 2019; Pages 261.e1-261.e9.
4. Cormio L., De Siati M., Lorusso F., Selvaggio O., Mirabella L., Sanguedolce F., Carrieri G. Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction. *Urology*. 2011 Jan;77(1):119-22.
5. Curis E., Nicolis I., Moinard C., Osowska S., Zerrouk N., Benazeth S., Cynober L. Almost all about citrulline in mammals. *Amino Acids*. 2005;29(3):177-205.
6. Cutrufello P.T., Gadowski S.J., Zavorsky G.S. The effect of L-citrulline and watermelon juice supplementation on anaerobic and aerobic exercise performance. *J Sports Sci*. 2015; 33(14):1459-66.
7. Figueroa A., Wong A., Jaime S.J., Gonzales J.U. Influence of L-citrulline and watermelon supplementation on vascular function and exercise performance. *Curr Opin Clin Nutr Metab Care*. 2017 Jan; 20(1):92-98.
8. Gonzalez A.M., Trexler E.T. Effects of Citrulline Supplementation on Exercise Performance in Humans: A Review of the Current Literature. *J Strength Cond Res*. 2020 May; 34(5):1480-1495.
9. Hotta Y., Shiota A., Kataoka T., Motonari M., Maeda Y., Morita M., Kimura K. Oral L-citrulline supplementation improves erectile function and penile structure in castrated rats. *Int J Urol*. 2014 Jun;21(6):608-12.
10. Huerta Ojeda Á, Domínguez de Hanna A, Barahona-Fuentes G. Efecto de la suplementación de L-arginina y L-citrulinasobre el rendimiento físico: una revisión sistemática [The effect of supplementation with L-arginine and L-citrulline on physical performance: a systematic review]. *Nutr Hosp*. 2019 Dec 26; 36(6):1389-1402. Spanish.
11. Jagim A.R., Harty P.S., Camic C.L. Common Ingredient Profiles of Multi-Ingredient Pre-Workout Supplements. *Nutrients*. 2019 Jan 24;11(2):254.
12. Kiyici F., Eroğlu H., Kishali N. F., Burmaoglu G. (2017). The Effect of Citrulline/Malate on Blood Lactate Levels in Intensive Exercise. *Biochemical Genetics*. 2017; 55(5-6), 387-394.
13. Lamprecht M. Acute Topics in Sport Nutrition. *Med Sport Sci*. Basel, Karger, 2012, vol 59, pp 18-28. DOI: 10.1159/000341937.
14. Martínez-Sánchez A., Alacid F., Rubio-Arias J.A., Fernández-Lobato B., Ramos-Campo D.J., Aguayo E. Consumption of Watermelon Juice Enriched in L-Citrulline and Pomegranate Ellagitannins Enhanced Metabolism during Physical Exercise. *J Agric Food Chem*. 2017 Jun 7; 65(22):4395-4404.
15. Mathews N.M. Prohibited Contaminants in Dietary Supplements. *Sports Health*. 2018 Jan/Feb;10(1):19-30.
16. Maughan R.J., Depiesse F., Geyer H. International Association of Athletics Federations. The use of dietary supplements by athletes. *J Sports Sci*. 2007; 25 Suppl 1:S103-13.
17. Moinard C., Nicolis I., Neveux N., Darquy S., Bénazeth S., Cynober L. Dose-ranging effects of citrulline administration on plasma amino acids and hormonal patterns in healthy subjects: the Citrudose pharmacokinetic study. *Br J Nutr*. 2008; 99(4):855-62.
18. Ochiai M., Hayashi T., Morita M., Ina K., Maeda M., Watanabe F., Morishita K. Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men. *Int J Cardiol*. 2012; 155(2):257-61.
19. Papadia C., Osowska S., Cynober L., Forbes A. Citrulline in health and disease. Review on human studies. *Clin Nutr*. 2018 Dec; 37(6 Pt A):1823-1828.
20. Pérez-Guisado J., Jakeman P.M. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. *J Strength Cond Res* 2010 May; 24(5):1215-22.
21. Rhim H.C., Kim S.J., Park J., Jang K.M. Effect of citrulline on post-exercise rating of perceived exertion, muscle soreness, and blood lactate levels: A systematic review and meta-analysis. *J Sport Health Sci*. 2020 Dec; 9(6):553-561.
22. Rogers J.M., Gills J., Gray M. Acute effects of Nitrosigine® and citrulline malate on vasodilation in young adults. *J Int Soc Sports Nutr*. 2020 Feb 24;17(1):12.
23. Shiota A., Hotta Y., Kataoka T., Morita M., Maeda Y., Kimura K. Oral L-citrulline supplementation improves erectile function in rats with acute arteriogenic erectile dysfunction. *J Sex Med*. 2013 Oct; 10(10):2423-9.
24. Smith H.A., Canter J.A., Christian K.G., Drinkwater D.C., Scholl F.G., Christman B.W., Rice G.D., Barr F.E., Summar M.L. Nitric oxide precursors and congenital heart surgery: a randomized controlled trial of oral citrulline. *J Thorac Cardiovasc Surg*. 2006 Jul; 132(1):58-65.
25. Sureda A., Córdova A., Ferrer M.D., Pérez G., Tur J.A., Pons A. L-citrulline-malate influence over branched chain amino acid utilization during exercise. *Eur J Appl Physiol*. 2010 Sep;110(2):341-51.
26. Sureda A., Pons A. Arginine and citrulline supplementation in sports and exercise: ergogenic nutrients? *Med Sport Sci*. 2012; 59:18-28.
27. Trexler E.T., Persky A.M., Ryan E.D., Schwartz T.A., Stoner L., Smith-Ryan A.E. Acute Effects of Citrulline Supplementation on High-Intensity Strength and Power Performance: A Systematic Review and Meta-Analysis. *Sports Med*. 2019 May; 49(5):707-718.
28. Tscholl P., Alonso J.M., Dollé G., Junge A., Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med*. 2010 Jan; 38(1):133-40. DOI: 10.1177/0363546509344071. Epub 2009 Oct 7. PMID: 19812387.
29. Valenzuela P.L., Morales J.S., Emanuele E., Pareja-Galeano H., Lucia A. Supplements with purported effects on muscle mass and strength. *Eur J Nutr*. 2019 Dec; 58(8):2983-3008.
30. Wijnands K.A.P., Castermans T.M.R., Hommen M.P.J., Meesters D.M., Poeze M. Arginine and Citrulline and the immune response in sepsis. *Nutrients*. 2015;7: 1426-63.

## СВЕДЕНИЯ ОБ АВТОРАХ:

Безуглов Эдуард Николаевич (Bezuglov Ehdvard Nikolaevich) – кандидат медицинских наук, доцент, доцент кафедры спортивной медицины и медицинской реабилитации Первого МГМУ им. И.М. Сеченова, ООО «Клиника спортивной медицины «Смарт Рекавери», Лаборатория спорта высших достижений Московского университета имени Витте, Научно-технический университет «Сириус»; 121552, г. Москва, ул. Крылатская, д. 10; e-mail: e.n.bezuglov@gmail.com; ORCID: 0000-0003-3828-0506.

Пирмаханов Бекжан Анатольевич (Pirmakhanov Bekzhan Anatolevich) – кандидат медицинских наук, ассистент кафе-дры эпидемиологии, биостатистики и доказательной медицины, факультет медицины и здравоохранения, Казахский национальный университет им. Аль-Фараби, Алма-Ата, Казахстан, Футбольный клуб «Кайрат», Алма-Ата, Казахстан; Республика Казахстан, г. Алматы, 050038, пр. аль-Фараби, 71; ректорат КазНУ им. аль-Фараби; e-mail: pirmakhanov.b@gmail.com; ORCID: 0000-0002-1512-8141.

Талибов Олег Букарович (Talibov Oleg Bukarovich) – кандидат медицинских наук, доцент, доцент кафедры терапии, клинической фармакологии и скорой медицинской помощи Московского государственного медико-стоматологиче-ского университета им. А.И. Евдокимова; Лаборатория спорта высших достижений Московского университета име-ни Витте, Научно-технический университет «Сириус»; 127473, Москва, улица Делегатская, 20/ СТР.1.; e-mail: oleg.talibov@gmail.com; ORCID: 0000-0001-6381-2450.

Иванов Кирилл Владимирович (Ivanov Kirill Vladimirovich) – врач по спортивной медицине Футбольного клуба «Рубин»; 420036, г. Казань, ул. Копылова, д. 2; e-mail: kirill-ivanov@yandex.ru; ORCID: 0000-0003-2836-4343.

Тахавиева Фарида Вазиховна (Takhavieva Farida Vazikhovna) – доктор медицинских наук, профессор, профессор кафедры неврологии и реабилитации Казанского государственного медицинского университета; 420012, г. Казань, ул. Бутлерова, д.49; e-mail: fartah@list.ru; ORCID: 0000-0002-7387-8944.

Бутовский Михаил Сергеевич (Butovskii Mikhail Sergeevich) – кандидат медицинских наук, ассистент кафедры невро-логии и реабилитации Казанского государственного медицинского университета, главный врач Футбольного клуба «Рубин»; 420036, г. Казань, ул. Копылова, д. 2; e-mail: dr mike81@inbox.ru; ORCID: 0000-0003-1295-9457.

Борисова Алена Владимировна (Borisova Alena Vladimirovna) – кандидат медицинских наук, ассистент кафедры не-врологии и реабилитации Казанского государственного медицинского университета, зав. медицинской службой Ака-демии Футбольного клуба «Рубин»; 420036, г. Казань, ул. Копылова, д. 2.; e-mail: doc-borisova@bk.ru; ORCID: 0000-0002-6786-0510.

Поступила в редакцию 11 октября 2022 г.

Принято к публикации 10 ноября 2022 г.

## ОБРАЗЕЦ ЦИТИРОВАНИЯ

Citrulline in elite sports: is there a point? / Bezuglov E.N., Pirmakhanov B.A., Talibov O.B., Ivanov K.V., Takhavieva F.V., Butovskii M.S., Borisova A.V. // Наука и спорт: современные тенденции. – 2022. – Т. 10, № 4. – С. 25-35. DOI: 10.36028/2308-8826-2022-10-4-25-35

## FOR CITATION

Bezuglov E.N., Pirmakhanov B.A., Talibov O.B., Ivanov K.V., Takhavieva F.V., Butovskii M.S., Borisova A.V. Citrulline in elite sports: is there a point? Science and sport: current trends., 2022, vol. 10, no.4, pp. 25-35. (in Russ.) DOI: 10.36028/2308-8826-2022-10-4-25-35