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L-arginine Supplementation in Endurance Athletes: A Systematic Review of Recovery Mechanisms and Performance Enhancement

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Abstract

L-arginine, a semi-essential amino acid, has garnered significant attention for its potential to enhance athletic performance, particularly within endurance sports. Recognized for its multifaceted roles in cardiovascular, immune, and metabolic functions, L-arginine serves as a precursor to biologically active molecules, including nitric oxide (NO), creatine, and polyamines, which are integral to muscle function and recovery. Through its ability to stimulate NO production, L-arginine promotes vasodilation, enhancing blood flow and oxygen delivery to active muscles, thereby improving exercise efficiency and endurance. Additionally, L-arginine influences muscle protein synthesis (MPS) via activation of the mTOR signaling pathway, aids in ammonia detoxification within the urea cycle, and supports cellular energetics by facilitating ATP production. These mechanisms collectively underscore its potential to support prolonged physical exertion, reduce muscle fatigue, and expedite post-exercise recovery. This systematic review examines current evidence on L-arginine supplementation in endurance athletes, focusing on its physiological impacts, mechanisms of action, and potential to enhance recovery and performance. Despite promising findings, variability in individual responses and mixed results across studies highlight the need for refined dosing strategies and further research into long-term safety and efficacy. This review

provides a comprehensive overview of L-arginine's potential as a supplement in sports nutrition, aiming to inform evidence-based recommendations for its application in endurance training and recovery strategies.

Introduction

L-arginine is a semi-essential amino acid recognized for its extensive roles in cellular metabolism, with particular interest for its implications in athletic performance, especially within endurance sports. This amino acid, vital for cardiovascular, immune, and metabolic functions, is naturally present in a variety of foods. Key sources include poultry and meats like turkey and pork, as well as seafood such as salmon and tuna. Nuts and seeds, including pumpkin seeds and almonds, legumes like chickpeas and lentils, whole grains, and dairy products also provide this nutrient along with other health-supporting components. Each of these foods contributes additional valuable nutrients beneficial to overall health. (1). Arginine serves not only as a building block for proteins but also as a precursor to a range of biologically significant molecules, including nitric oxide (NO), urea, polyamines, proline, glutamate, creatine, and agmatine. Among these, nitric oxide is particularly notable for its function as a vasodilator, enhancing blood flow and, consequently, the oxygen supply to active muscles, which is a fundamental mechanism that may improve exercise performance and endurance. (2).

The metabolism of arginine involves complex enzymatic pathways regulated by enzymes such as argininosuccinate synthase, the arginase isoenzymes, nitric oxide synthase (NOS) isoforms, and arginine decarboxylase. These enzymes govern key steps in both the synthesis and degradation of arginine, determining its metabolic fate within the body. (3) For endurance athletes, the ability to modulate nitric oxide levels through L-arginine supplementation presents a promising avenue for enhancing blood flow, nutrient delivery, and oxygen availability, all of which are critical for prolonged physical exertion. (4).

The interest in L-arginine supplementation in sports is driven by its potential to improve performance through the expansion of vascular function, as well as its roles in the synthesis of creatine and polyamines, which contribute to muscle performance and repair. Research has highlighted that the manipulation of arginine metabolism could support recovery post-exercise, decrease muscular fatigue, and even support immune function—factors particularly relevant to endurance athletes. (5).

Thus, this review aims to systematically evaluate the literature regarding L-arginine's effects on endurance performance and recovery, offering a nuanced understanding of its physiological roles, the regulatory mechanisms involved in its metabolism, and the potential for its strategic application in sports nutrition and endurance training. Through a rigorous synthesis of current findings, this work seeks to provide evidence-based insights into how L-arginine supplementation may support enhanced athletic performance and recovery.

Mechanism of action

The mechanism of action of arginine encompasses multiple physiological pathways, primarily through its role as a precursor for nitric oxide (NO) synthesis. (6) Arginine is metabolized by nitric oxide synthase (NOS) to produce NO, a potent vasodilator that plays a crucial role in vascular function. This biochemical pathway leads to improved blood flow, which consequently enhances nutrient transport and metabolic waste removal.(7) The NO-mediated vasodilation also contributes to increased blood flow to various tissues, including the placenta, potentially improving fetal development.(6) Arginine stimulates growth hormone (GH) release by inhibiting somatostatin secretion and potentially stimulating growth hormone-releasing hormone neurons. This increased GH secretion enhances protein synthesis, lipolysis, and anabolic activity. Consequently, arginine-induced GH elevation may improve muscle growth, fat metabolism, and tissue repair, with significant implications for exercise physiology and metabolic health.(8)

Furthermore, arginine influences energy metabolism by serving as a substrate for the synthesis of creatine, an important molecule in cellular energy transfer. The physiological effects of arginine extend beyond vascular function, as it is involved in protein synthesis and cell proliferation through the mammalian target of rapamycin (mTOR) signaling pathway. (9) This multifaceted mechanism of action underscores arginine's potential to modulate trophoblast cell function, placental development, and overall fetal growth. (10)

L-arginine serves as a key precursor for nitric oxide (NO) synthesis, a process catalyzed by nitric oxide synthase (NOS). NO acts as a potent vasodilator, relaxing vascular smooth muscle cells and thereby enhancing blood flow and oxygen delivery to tissues. This effect is particularly advantageous under conditions where increased tissue perfusion is needed, such as during physical exertion or in states of compromised circulation. Through its

vasodilatory action, L-arginine supports improved cardiovascular function and nutrient delivery to active tissues, optimizing both performance and recovery.(11)

Within the urea cycle, L-arginine plays an essential role in the detoxification of ammonia, a byproduct of protein metabolism. By facilitating the conversion of ammonia into urea, which is then excreted in the urine, L-arginine helps prevent the buildup of toxic nitrogenous waste. This detoxifying function is particularly important in high-protein diets and intense physical activity, where ammonia production may increase, making L-arginine crucial for maintaining nitrogen balance and metabolic health. (12)

L-arginine significantly contributes to cellular energetics by enhancing mitochondrial function and ATP production. It supports mitochondrial respiration through NO-mediated pathways, which regulate bioenergetics and improve ATP synthesis. This increase in cellular energy availability is critical for sustaining high metabolic demands, particularly in muscle cells during prolonged physical activity. The enhanced ATP production associated with L-arginine supplementation aids in cellular function and endurance, highlighting its value in energy-intensive physiological states. (13)

L-arginine also demonstrates protective effects against oxidative stress by modulating levels of reactive oxygen species (ROS). It enhances the activity of key antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), which act to neutralize ROS and prevent oxidative damage to cellular components. Through these antioxidant mechanisms, L-arginine supports cellular resilience, reduces oxidative injury, and contributes to overall tissue health, particularly under conditions of heightened oxidative stress such as intense physical exertion. (14)

L-arginine and performance in endurance sports

Key findings from the study indicate that acute supplementation with 6 g of L-arginine enhances nitric oxide (NO) synthesis, resulting in reduced oxygen consumption (VO2) during moderate-intensity exercise and a decreased VO2 slow component during severe-intensity exercise. Additionally, it improves exercise efficiency and tolerance, likely through increased muscle oxygen supply and direct effects on muscle contractile efficiency and mitochondrial function. (15)

The investigation revealed that supplements containing arginine (1.5 or 3.0 g) led to notably higher PWCFT values post-supplementation compared to the placebo group. This

improvement is likely linked to decreased levels of metabolic byproducts, such as lactate and ammonia, as well as enhanced blood circulation due to increased nitric oxide synthesis and reduced endothelin production following the supplementation with arginine and grape seed extract.(16)

L-arginine may contribute to delayed fatigue by influencing blood lactate levels and respiratory metabolic indices. It has been commonly reported that supplementation with L-arginine can enhance athletic performance during sports activities (17). Additionally, Yaman et al. observed that L-arginine supplementation led to a significant reduction in blood pressure and an increase in VO2 max, suggesting a positive impact on athletic performance capacity (18) .

According to the research by Viribay et al. (2020), supplementation with arginine may positively influence physical performance outcomes in both anaerobic and aerobic tests. An acute dosage of approximately 0.15 g/kg (around 10–11 g) taken 60–90 minutes prior to exercise is suggested for enhancing performance across various disciplines. Furthermore, a chronic intake of 1.5–2 g/day for 4–7 days, or 10–12 g/day over 8 weeks, also showed beneficial effects on athletic performance. (19)

L-arginine supplementation has been studied for its potential to enhance endurance performance, particularly in competitive cycling. This research specifically focused on the acute effects of L-arginine on a 20 km time trial, emphasizing real-world performance rather than just physiological markers. While the exact outcomes were not disclosed, the potential of L-arginine to increase nitric oxide production may improve blood flow and oxygen delivery during exercise, although results can vary based on dosage, timing, and participant fitness levels.(20)

The results of the recent investigation highlight the substantial impact of short-term sprint interval training (SIT) on skeletal muscle adaptations over a two-week period. Specifically, there was a significant increase in muscle glycogen content by approximately 50%, coupled with enhanced oxidative capacity indicated by a notable rise in citrate synthase activity (21). Additionally, the training regimen elevated the active form of pyruvate dehydrogenase, improving the muscle’s ability to oxidize pyruvate. Importantly, reductions in net glycogenolysis and lactate accumulation were observed, alongside a 9.6% improvement in cycling performance during time trials.(22)

A supplement containing L-arginine and antioxidants has been shown to enhance the anaerobic threshold and the work performed at this threshold in older cyclists over a period of

three weeks, with no observed changes in VO2 max. These results suggest that L-arginine and antioxidant supplementation may play a significant role in improving exercise performance among the elderly (23). Using high-intensity interval training in combination with L-Arginine lead to improvement of aerobic and anaerobic fitness in women futsal players (24). A well-balanced diet rich in L-arginine is crucial for maintaining overall health, as this amino acid supports nitric oxide production, vascular health, and immune response. Foods high in bioavailable L-arginine include meats like turkey breast, chicken, and pork loin, as well as seafood varieties such as salmon, shrimp, and tuna, which also provide omega-3 fatty acids. Plant-based sources like nuts, legumes, whole grains, and dairy products offer alternative options, providing fiber, micronutrients, and moderate levels of L-arginine. Together, these food groups facilitate the integration of L-arginine into one's diet, promoting metabolic and cardiovascular well-being. (25)

Effect of L-arginine supplementation on regenerative mechanisms

1. *Nitric oxide synthesis*

L-arginine functions as a pivotal precursor for the synthesis of nitric oxide (NO) during muscle regeneration. NO, produced by nitric oxide synthases (NOS), is fundamental for the activation of satellite cells, myogenesis, and angiogenesis in the process of muscle repair (26). It regulates multiple factors involved in the regeneration of skeletal muscle following eccentric contractions, impacting muscle damage, leukocyte infiltration, and the expression of regenerative gene markers such as MyoD and myogenin (27). Supplementation with L-arginine can augment NO synthesis, thereby enhancing blood flow to tissues, including skeletal muscle (28). This increased production of NO may potentially support muscle recovery, immune function, and overall exercise performance. However, the efficacy of L-arginine supplementation in promoting NO synthesis and subsequent improvements in exercise performance has demonstrated mixed results in some studies (29). Nonetheless, L-arginine remains a crucial component in NO-mediated mechanisms of muscle regeneration.

2. *Muscle protein metabolism + MPS*

L-arginine (L-Arg) plays a pivotal role in enhancing muscle protein metabolism and stimulating muscle protein synthesis (MPS) through the activation of the mechanistic target of

rapamycin (mTOR) signaling pathway. Research has demonstrated that L-Arg supplementation significantly increases protein synthesis while simultaneously reducing protein degradation across various cell types, including C2C12 muscle cells, porcine trophectoderm cells, and chicken intestinal epithelial cells (30). This anabolic effect is mediated by the phosphorylation of key components of the mTOR pathway, namely mTOR itself, p70S6K, and 4E-BP1, which are critical regulators of protein synthesis and muscle hypertrophy (31). Additionally, L-Arg facilitates the activation of mTOR through both nitric oxide (NO)-dependent and independent mechanisms, further promoting anabolic processes and cellular proliferation (32). In C2C12 muscle cells, for instance, L-Arg-induced activation of the mTOR/p70S6K pathway was shown to be NO-dependent, highlighting the multifaceted role of L-Arg in muscle metabolism (33). Beyond protein synthesis, L-Arg also enhances mitochondrial bioenergetics and DNA synthesis via the PI3K-Akt pathway, contributing to improved cellular energy metabolism and overall muscle function (34).

3. *Reduction of inflammation*

L-arginine supplementation has shown promising antioxidant effects in various studies. In skeletal muscle cells, L-arginine reduced superoxide production and improved antioxidant enzyme activity and expression (35). In rat heart tissue, L-arginine intake increased glutathione peroxidase (GPX) and total antioxidant capacity (TAC) (36). Human studies with ischemic heart disease patients demonstrated that L-arginine supplementation increased superoxide dismutase (SOD) activity, total thiols, and plasma ascorbic acid levels while decreasing lipid peroxidation, carbonyl content, and xanthine oxidase activity (37). These effects were attributed to L-arginine's role as a free radical scavenger and its ability to inhibit pro-oxidant enzymes, mediated by nitric oxide production.

4. *Removal of metabolic products*

Arginine supplementation has shown promising effects on exercise performance and recovery. Studies indicate that it can reduce ammonia levels during high-intensity exercise (38), potentially delaying fatigue. Arginine also appears to modulate lymphocyte levels, suggesting a link between ammonia metabolism and immune function (39). In fish, arginine plays roles in ureagenesis, immune function, and ammonia detoxification (40). For athletes, arginine supplementation may accelerate lactic acid removal, decrease body fat, and improve

anaerobic performance. It has been shown to reduce resting heart rate and recovery heart rate, as well as decrease levels of certain enzymes associated with muscle damage (41) While these findings are promising, more research is needed to fully understand arginine's effects on antioxidant systems, immune responses, and ammonia detoxification mechanisms across different species and conditions (40).

5. *Regeneration of muscle tissue*

L-arginine plays a crucial role in cell proliferation and tissue regeneration. It enhances fibroblast and endometrial cell proliferation while reducing apoptosis (42). This amino acid stimulates cell growth through various signaling pathways, including GPRC6A-ERK1/2, PI3K/Akt, and NF-κB (43). L-arginine serves as a substrate for nitric oxide (NO) synthesis, which is essential for wound healing. Additionally, it can be metabolized to produce proline and polyamines, supporting collagen synthesis and cellular proliferation (44). In wound healing, L-arginine supplementation enhances fibroblast survival and proliferation, crucial for new tissue formation (45). Its effects on increasing the Bcl2/Bax ratio and modulating various kinases further support its role in promoting cell survival and proliferation (46). These findings highlight L-arginine's potential in regenerative medicine and wound healing applications.

6. *Subjective indicators of physical recovery*

Recovery assessment encompasses both objective and subjective indicators, with growing emphasis on patient-centered perspectives (47). Objective indicators include symptom severity, level of functioning, and performance measures, while subjective indicators focus on patient-reported outcomes such as quality of life, empowerment, and personal confidence (48). Research shows that objective and subjective recovery measures are not always directly correlated, suggesting they are complementary rather than synonymous (49). Subjective indicators of recovery identified by patients, family members, and clinicians include returning to work, resuming family roles, achieving independence, and recapturing normality (50). Factors such as social support, loneliness, and quality of life can influence subjective recovery perceptions (51). While patient-reported outcomes prioritize the individual's perspective, they may be susceptible to response shift and recall bias (47). Ideally,

recovery assessment should combine both objective and subjective measures for a comprehensive evaluation.

Side effects of Arginine

Gastrointestinal Disorders

Oral supplementation of arginine is associated with gastrointestinal (GI) effects, particularly when administered at high, single doses. Arginine and citrulline increase local nitric oxide (NO) production in the small intestine, which can disrupt normal intestinal physiology and lead to gastrointestinal toxicity under specific conditions.(52). Unlike other dibasic amino acids like lysine or ornithine, L-arginine specifically induces water and electrolyte secretion via NO, acting as an absorbagogue at low concentrations but a secretagogue at high concentrations. This NO-mediated action is also linked to the laxative effects observed with certain substances, and there are documented cases of diarrhea following oral arginine administration. (53). Clinical data report a wide range of arginine intakes, from 3 g/d to more than 100 g/d, with variable standards in reporting adverse GI effects, including nausea, vomiting, and diarrhea. (54). Single doses of 3–6 g seldom cause side effects, although doses above 9 g have induced gastrointestinal symptoms, particularly in healthy athletes, who appear more susceptible than individuals with diabetes.(55). For most adults, arginine-related side effects tend to manifest at doses exceeding 140 mg/kg in single intakes and are more pronounced when part of a daily regimen exceeding approximately 30 g/d. Adverse effects such as diarrhea often diminish when arginine doses are divided throughout the day, unlike other substances like lactitol, a non-absorbed disaccharide alcohol with a similar laxative threshold. (56). Overall, these findings indicate that the gastrointestinal tolerability of arginine supplementation is highly dose-dependent.

Effects on BP and cardiovascular system,

Recent studies have investigated the impact of L-arginine supplementation on post-exercise hypotension in hypertensive individuals. A single dose of 8g L-arginine before aerobic exercise induced significant post-exercise systolic hypotension in hypertensive patients (57). This effect was observed in most participants, highlighting inter-individual responsiveness (58). In elderly women, L-arginine supplementation combined with exercise led to significant decreases in systolic blood pressure at various time points post-exercise (59).

While L-arginine alone did not significantly change blood pressure, it improved diastolic post-exercise hypotension when combined with exercise in hypertensive individuals (60). These studies suggest that L-arginine supplementation may enhance post-exercise hypotension effects, particularly when combined with aerobic exercise, potentially offering a beneficial strategy for blood pressure management in hypertensive patients.

Electrolyte disorders

L-arginine supplementation has shown both beneficial and potentially adverse effects on electrolyte balance. In rats with myocardial injury, L-arginine reversed electrolyte imbalances, increasing serum levels of Na+, Cl-, and HCO3- (61). While it can increase nitric oxide production in the small intestine, potentially causing water and electrolyte secretion (62) , its impact on sodium balance is not directly addressed in these papers. In critically ill patients, disorders of sodium balance are common and often iatrogenic, potentially contributing to increased morbidity and mortality (63) . The effectiveness of arginine supplementation may depend on endogenous levels of asymmetric dimethylarginine (ADMA), with benefits observed in subjects with high ADMA levels (64) .

Allergic reactions and immune system

Adverse effects on the immune system from L-arginine supplementation appear minimal, with evidence supporting its role in enhancing immune responses, particularly by promoting CD4+ lymphocyte proliferation and reducing infection rates in immunocompromised individuals. Clinical trials reviewed indicate no significant adverse effects on the immune system, suggesting that L-arginine acts as an immunomodulator (65). This modulation is primarily achieved through the regulation of nitric oxide (NO) pathways, which may exert beneficial or neutral effects depending on the physiological context. In terms of allergic reactions, meta-analyses found no evidence of allergies associated with L-arginine supplementation. Reported side effects primarily involve gastrointestinal disturbances, such as diarrhea, rather than immunologically driven allergic responses.(66). These findings suggest a favorable safety profile for L-arginine in immunological applications, with no apparent risk of immune hypersensitivity.

Drug interactions

The research papers discuss various aspects of drug interactions and formulations involving arginine and other compounds. Perindopril arginine, when combined with amlodipine in a fixed-dose tablet, showed no significant pharmacokinetic interactions in healthy volunteers (67). This combination demonstrated effectiveness in lowering blood pressure and reducing cardiovascular risks, with common side effects including peripheral edema and cough (68). Arginine, as an amino acid, can form co-amorphous mixtures with poorly water-soluble drugs like carbamazepine and indomethacin, potentially stabilizing the amorphous form and enhancing dissolution through specific molecular interactions (69). Research on drug interactions between arginine and spironolactone reveals complex effects on cardiovascular function. Spironolactone, an aldosterone receptor antagonist, inhibits the activation of the L-arginine/iNOS/NO pathway in aortic adventitia of hypertensive rats (70). Both spironolactone and eplerenone increase endothelial arginine transport and nitric oxide generation by modulating the cationic amino acid transporter-1 (CAT-1) in endothelial cells (71). In L-NAME-induced hypertension, spironolactone and L-arginine can reverse left ventricular hypertrophy and aortic remodeling (72). However, while L-arginine treatment normalizes protein concentrations in the left ventricle, spironolactone treatment results in persistently elevated levels of metabolic, contractile, and insoluble collagenous proteins compared to controls (73). These findings suggest that spironolactone and arginine have distinct but potentially complementary effects on cardiovascular remodeling and function in hypertensive conditions.

Safety of chronic dietary arginine supplementation

Research on the safety and efficacy of chronic arginine supplementation presents mixed findings. While some studies suggest that arginine supplementation is generally safe and well-tolerated in various populations, with potential benefits for metabolic health (6), others raise concerns about long-term use, particularly in older individuals. (14), found that chronic arginine supplementation may accelerate kidney aging and increase mortality in older mice. Safety thresholds have been proposed with (6). estimating that humans could tolerate up to 15 g/day of enteral arginine supplementation. However, (74) found little evidence supporting arginine's benefits for athletic performance or recovery. Short-term use may cause gastrointestinal and cardiovascular side effects. The conflicting results highlight the need for

further research, especially regarding long-term safety and efficacy in different age groups and health conditions.

Conclusion

L-arginine supplementation shows promising potential for enhancing performance and recovery in endurance athletes through multiple physiological mechanisms, including increased nitric oxide (NO) production, improved vascular function, and support of muscle regeneration. This systematic review highlights L-arginine's role in stimulating NO synthesis, which promotes vasodilation, enhancing blood flow and oxygen delivery to active muscle tissues. Such effects contribute to greater exercise efficiency, reduced muscle fatigue, and enhanced endurance, which are essential for athletes engaging in prolonged physical exertion. Additionally, L-arginine serves as a precursor in the synthesis of creatine, polyamines, and proline, supporting protein synthesis, cellular repair, and energy production pathways integral to muscle recovery. The regulatory role of L-arginine in cellular energetics and the urea cycle underscores its ability to facilitate ammonia detoxification and ATP production, both critical in managing metabolic demands during intense exercise. Moreover, L-arginine exhibits antioxidant properties, modulating reactive oxygen species (ROS) and promoting the activity of antioxidant enzymes, thus protecting against exercise-induced oxidative stress and potentially improving immune resilience in athletes.However, despite these positive findings, the review also identifies limitations and conflicting results within the literature. While L-arginine appears to support athletic performance and recovery, some studies report minimal impact or variability in individual responses, highlighting the need for personalized dosing strategies. Gastrointestinal side effects, particularly at high single doses, emphasize the importance of dosage regulation and the potential benefit of divided intakes. In conclusion, L-arginine holds substantial promise as a supplement to enhance endurance performance and recovery, though further research is essential to refine dosage protocols, assess long-term safety, and confirm its efficacy across varied athletic populations. These insights can inform evidence-based recommendations for L-arginine's strategic application in sports nutrition, contributing to optimized training outcomes and supporting the health and performance goals of endurance athletes.

Disclosure

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Bibliography:

1. Aitken, L. M., Chaboyer, W., Jeffrey, C., Martin, B., Whitty, J. A., Schuetz, M., & Richmond, T. S. (2016). Indicators of injury recovery identified by patients, family members and clinicians. *Injury*, *47*(12), 2655–2663. https://doi.org/10.1016/j.injury.2016.10.006
2. Bailey, S. J., Winyard, P. G., Vanhatalo, A., Blackwell, J. R., DiMenna, F. J., Wilkerson, D. P., & Jones, A. M. (2010). Acute l-arginine supplementation reduces

the O2 cost of moderate-intensity exercise and enhances high-intensity exercise tolerance. *Journal of Applied Physiology*, *109*(5), 1394–1403. https://doi.org/10.1152/japplphysiol.00503.2010

3. Botchlett, R., Lawler, J. M., & Wu, G. (2018). L-Arginine and L-Citrulline in sports nutrition and health. In *Elsevier eBooks*(pp. 645–652). https://doi.org/10.1016/b978-0-12-813922-6.00055-2
4. Bowyer, A., & Royse, C. (2018). A matter of perspective – Objective versus subjective outcomes in the assessment of quality of recovery. *Best Practice & Research Clinical Anaesthesiology*, *32*(3–4), 287–294. https://doi.org/10.1016/j.bpa.2018.02.003
5. Brooks, J. R., Oketch-Rabah, H., Dog, T. L., Gorecki, D. K. J., Barrett, M. L., Cantilena, L., Chung, M., Costello, R. B., Dwyer, J., Hardy, M. L., Jordan, S. A., Maughan, R. J., Marles, R. J., Osterberg, R. E., Rodda, B. E., Wolfe, R. R., Zuniga, J. M., Valerio, L. G., Jones, D., . . . Sarma, N. D. (2016). Safety and performance benefits of arginine supplements for military personnel: a systematic review. *Nutrition Reviews*, *74*(11), 708–721. https://doi.org/10.1093/nutrit/nuw040
6. Burgomaster, K. A., Heigenhauser, G. J. F., & Gibala, M. J. (2006). Effect of short-term sprint interval training on human skeletal muscle carbohydrate metabolism during exercise and time-trial performance. *Journal of Applied Physiology*, *100*(6), 2041–2047. https://doi.org/10.1152/japplphysiol.01220.2005
7. Camic, C. L., Housh, T. J., Zuniga, J. M., Hendrix, R. C., Mielke, M., Johnson, G. O., & Schmidt, R. J. (2010). Effects of Arginine-Based supplements on the physical working capacity at the fatigue threshold. *The Journal of Strength and Conditioning Research*, *24*(5), 1306–1312. https://doi.org/10.1519/jsc.0b013e3181d68816
8. Casonatto, J., & Cavalari, J. V. (2022). A single dosage of L-Arginine oral supplementation induced Post-Aerobic exercise hypotension in hypertensive patients. *Journal of Dietary Supplements*, *20*(5), 735–748. https://doi.org/10.1080/19390211.2022.2106006
9. Casonatto, J., Enokida, D. M., & Grandolfi, K. (2019). Inter-Individual Responses to Citrulline Malate Oral Supplementation on Post-Exercise Hypotension in Hypertensives: A 24-Hour analysis. *Arquivos Brasileiros De Cardiologia*. https://doi.org/10.5935/abc.20190115

10. Casonatto, J., Zago, D. M., Enokida, D. M., Grandolfi, K., & Aguiar, A. F. (2019). L-Arginine supplementation improves post-exercise hypotension in elderly women. *Revista Brasileira De Medicina Do Esporte*, *25*(4), 333–337. https://doi.org/10.1590/1517-869220192504182865
11. Chen, S., Kim, W., Henning, S. M., Carpenter, C. L., & Li, Z. (2010). Arginine and antioxidant supplement on performance in elderly male cyclists: a randomized controlled trial. *Journal of the International Society of Sports Nutrition*, *7*(1). https://doi.org/10.1186/1550-2783-7-13
12. Curran, J. N., Winter, D. C., & Bouchier-Hayes, D. (2006). Biological fate and clinical implications of arginine metabolism in tissue healing. *Wound Repair and Regeneration*, *14*(4), 376–386. https://doi.org/10.1111/j.1743-6109.2006.00151.x
13. Cynober, L., Bier, D. M., Kadowaki, M., Morris, S. M., Elango, R., & Smriga, M. (2016). Proposals for upper limits of safe intake for arginine and tryptophan in young adults and an upper limit of safe intake for leucine in the elderly. *Journal of Nutrition*, *146*(12), 2652S-2654S. https://doi.org/10.3945/jn.115.228478
14. De Lima, F. F., Da Silva, T. F., Neto, M. M., Toscano, L. T., Da Silva, C. S. O., & Silva, A. S. (2018). Effect of L-arginine intake on exercise-induced hypotension. *Nutrición Hospitalaria*, *35*(5), 1195. https://doi.org/10.20960/nh.1708
15. [Effect of spironolactone on L-arginine/iNOS/NO pathway of aortic adventitia in spontaneously hypertensive rats]. (2010, February 9). PubMed. https://pubmed.ncbi.nlm.nih.gov/20367944/
16. *Effects of N-acetylcysteine and L-arginine in the antioxidant system of C2C12 cells*. (2015, June 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/26205767/
17. [Efficacy comparison between 5 mg perindopril arginine salt and 4 mg perindopril tert-butylamine salt for patients with mild to moderate essential hypertension]. (2015, October 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/26652987/
18. Elango, R. (2023). Tolerable upper intake level for individual amino acids in humans: A narrative review of recent clinical studies. *Advances in Nutrition*, *14*(4), 885–894. https://doi.org/10.1016/j.advnut.2023.04.004
19. Elliott, W. J., & Bistrika, E. A. (2017). Perindopril arginine and amlodipine besylate for hypertension: a safety evaluation. *Expert Opinion on Drug Safety*, *17*(2), 207–216. https://doi.org/10.1080/14740338.2018.1397129

20. Fidanboylu, M., & Thomas, S. A. (2024). L-Arginine and asymmetric dimethylarginine (ADMA) transport across the mouse blood-brain and blood-CSF barriers: Evidence of saturable transport at both interfaces and CNS to blood efflux. *PLoS ONE*, *19*(10), e0305318. https://doi.org/10.1371/journal.pone.0305318
21. Fujiwara, T., Kanazawa, S., Ichibori, R., Tanigawa, T., Magome, T., Shingaki, K., Miyata, S., Tohyama, M., & Hosokawa, K. (2014). L-Arginine Stimulates Fibroblast Proliferation through the GPRC6A-ERK1/2 and PI3K/Akt Pathway. *PLoS ONE*, *9*(3), e92168. https://doi.org/10.1371/journal.pone.0092168
22. Gonçalves, L. C., Bessa, A., Freitas-Dias, R., Luzes, R., Werneck-De-Castro, J. P. S., Bassini, A., & Cameron, L. (2012). A sportomics strategy to analyze the ability of arginine to modulate both ammonia and lymphocyte levels in blood after high-intensity exercise. *Journal of the International Society of Sports Nutrition*, *9*(1). https://doi.org/10.1186/1550-2783-9-30
23. Greene, J. M., Feugang, J. M., Pfeiffer, K. E., Stokes, J. V., Bowers, S. D., & Ryan, P. L. (2013). L-arginine enhances cell proliferation and reduces apoptosis in human endometrial RL95-2 cells. *Reproductive Biology and Endocrinology*, *11*(1), 15. https://doi.org/10.1186/1477-7827-11-15
24. Grimble, G. K. (2007a). Adverse gastrointestinal effects of arginine and related amino acids. *Journal of Nutrition*, *137*(6), 1693S-1701S. https://doi.org/10.1093/jn/137.6.1693s
25. Grimble, G. K. (2007b). Adverse gastrointestinal effects of arginine and related amino acids. *Journal of Nutrition*, *137*(6), 1693S-1701S. https://doi.org/10.1093/jn/137.6.1693s
26. Hiratsu, A., Tataka, Y., Namura, S., Nagayama, C., Hamada, Y., & Miyashita, M. (2022). The effects of acute and chronic oral L-arginine supplementation on exercise-induced ammonia accumulation and exercise performance in healthy young men: A randomised, double-blind, cross-over, placebo-controlled trial. *Journal of Exercise Science & Fitness*, *20*(2), 140–147. https://doi.org/10.1016/j.jesf.2022.02.003
27. Hoseini, A., Dehnou, V. V., Azizi, M., & Alam, M. K. (2015). Effect of High-Intensity Interval Training (HIT) for 4 Weeks with and without L-Arginine Supplementation on the Performance of Women's Futsal Players. *Quarterly of Horizon of Medical Sciences*, *21*(2), 113–119. https://doi.org/10.18869/acadpub.hms.21.2.113

28. Hoseini, S. M., Khan, M. A., Yousefi, M., & Costas, B. (2020). Roles of arginine in fish nutrition and health: insights for future researches. *Reviews in Aquaculture*, *12*(4), 2091–2108. https://doi.org/10.1111/raq.12424
29. Huang, J., Ladeiras, D., Yu, Y., Ming, X., & Yang, Z. (2021). Detrimental effects of chronic L-Arginine rich food on aging kidney. *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/fphar.2020.582155
30. Juan, E., De Lucia, M., Beaud, V., Oddo, M., Rusca, M., Viceic, D., Clarke, S., & Rossetti, A. O. (2018). How do you feel? Subjective perception of recovery as a reliable surrogate of cognitive and functional outcome in cardiac arrest survivors. *Critical Care Medicine*, *46*(4), e286–e293. https://doi.org/10.1097/ccm.0000000000002946
31. Kalman, D., Harvey, P., Ojalvo, S. P., & Komorowski, J. (2016). Randomized prospective Double-Blind studies to evaluate the cognitive effects of Inositol-Stabilized Arginine silicate in healthy physically active adults. *Nutrients*, *8*(11), 736. https://doi.org/10.3390/nu8110736
32. Kang, K., Shu, X., Zhong, J., & Yu, T. (2014). Effect of L-arginine on immune function: a meta-analysis. *PubMed*, *23*(3), 351–359. https://doi.org/10.6133/apjcn.2014.23.3.09
33. Kong, X., Tan, B., Yin, Y., Gao, H., Li, X., Jaeger, L. A., Bazer, F. W., & Wu, G. (2011a). l-Arginine stimulates the mTOR signaling pathway and protein synthesis in porcine trophectoderm cells. *The Journal of Nutritional Biochemistry*, *23*(9), 1178–1183. https://doi.org/10.1016/j.jnutbio.2011.06.012
34. Kong, X., Tan, B., Yin, Y., Gao, H., Li, X., Jaeger, L. A., Bazer, F. W., & Wu, G. (2011b). l-Arginine stimulates the mTOR signaling pathway and protein synthesis in porcine trophectoderm cells. *The Journal of Nutritional Biochemistry*, *23*(9), 1178–1183. https://doi.org/10.1016/j.jnutbio.2011.06.012
35. Lagaye, S., Derrien, M., Menu, E., CoïTo, C., Tresoldi, E., MauclèRe, P., Scarlatti, G., Chaouat, G., Barré-Sinoussi, F., & Bomsel, M. (2001). Cell-to-Cell Contact Results in a Selective Translocation of Maternal Human Immunodeficiency Virus Type 1 Quasispecies across a Trophoblastic Barrier by both Transcytosis and Infection. *Journal of Virology*, *75*(10), 4780–4791. https://doi.org/10.1128/jvi.75.10.4780-4791.2001

36. Líndez, A. M. I., & Reith, W. (2021). Arginine-dependent immune responses. *Cellular and Molecular Life Sciences*, *78*(13), 5303–5324. https://doi.org/10.1007/s00018-021-03828-4
37. Lloyd, C., King, R., & Moore, L. (2009). Subjective and Objective Indicators of Recovery in Severe Mental Illness: a Cross-Sectional Study. *International Journal of Social Psychiatry*, *56*(3), 220–229. https://doi.org/10.1177/0020764009105703
38. Lomonosova, Y. N., Shenkman, B. S., Kalamkarov, G. R., Kostrominova, T. Y., & Nemirovskaya, T. L. (2014). L-arginine Supplementation Protects Exercise Performance and Structural Integrity of Muscle Fibers after a Single Bout of Eccentric Exercise in Rats. *PLoS ONE*, *9*(4), e94448. https://doi.org/10.1371/journal.pone.0094448
39. Morris, S. M. (2002). REGULATION OFENZYMES OF THEUREACYCLE ANDARGININEMETABOLISM. *Annual Review of Nutrition*, *22*(1), 87–105. https://doi.org/10.1146/annurev.nutr.22.110801.140547
40. Namba, H., Hamada, H., Kimura, T., Sekikawa, K., Kamikawa, N., Ishio-Ueoka, H., Kajiwara, T., Sato, Y. M., Aizawa, F., & Yoshida, T. (2022). Effects of L-arginine on impaired blood fluidity after high-intensity exercise: An in vitro evaluation. *Clinical Hemorheology and Microcirculation*, *82*(1), 1–12. https://doi.org/10.3233/ch-211201
41. Okon, I. A., Bes, J. A., Udoakag, I. S., Udia, J. P., & Owu, D. U. (2022). L-Arginine oral supplementation reverses hematological and electrolytes imbalances in Adrenaline-Induced myocardial injury in rats. *Journal of Medical Sciences(Faisalabad)*, *22*(3), 90–98. https://doi.org/10.3923/jms.2022.90.98
42. Paulis, L., Matuskova, J., Adamcova, M., Pelouch, V., Simko, J., Krajcirovicova, K., Potacova, A., Hulin, I., Janega, P., Pechanova, O., & Simko, F. (2008). Regression of left ventricular hypertrophy and aortic remodelling in NO-deficient hypertensive rats: effect of l-arginine and spironolactone. *Acta Physiologica*, *194*(1), 45–55. https://doi.org/10.1111/j.1748-1716.2008.01862.x
43. Poeggeler, B., Robenek, H., & Pappolla, M. A. (2021). Editorial: Pharmacology of L-Arginine and L-Arginine-Rich Food. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.743788
44. Powers, R. W., Chen, L., Russell, P. T., & Larsen, W. J. (1995). Gonadotropin-stimulated regulation of blood-follicle barrier is mediated by nitric oxide. *AJP*

Endocrinology and Metabolism, *269*(2), E290–E298. https://doi.org/10.1152/ajpendo.1995.269.2.e290

45. Pranskunas, A., Pranskuniene, Z., Bernatoniene, J., Vaitkaitiene, E., & Brazaitis, M. (2015). Microcirculatory effects of L-arginine during acute anaerobic exercise in healthy men: A pilot study. *Journal of Exercise Science & Fitness*, *13*(2), 57–62. https://doi.org/10.1016/j.jesf.2015.04.001
46. *Proliferative, anti-apoptotic and immune-enhancing effects of L-arginine in culture of skin fibroblasts*. (2017, September 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/28954469/
47. Ranchordas, M. K., & Whitehead, T. (2011). Effect of acute L-arginine supplementation on 20 km time trial performance in competitive male cyclists. *British Journal of Sports Medicine*, *45*(15), A11.2-A11. https://doi.org/10.1136/bjsports-2011-090606.35
48. Rezaei, S., Gholamalizadeh, M., Tabrizi, R., Nowrouzi-Sohrabi, P., Rastgoo, S., & Doaei, S. (2021). The effect of L-arginine supplementation on maximal oxygen uptake: A systematic review and meta-analysis. *Physiological Reports*, *9*(3). https://doi.org/10.14814/phy2.14739
49. Roe, D., Mashiach-Eizenberg, M., & Lysaker, P. H. (2011). The relation between objective and subjective domains of recovery among persons with schizophrenia-related disorders. *Schizophrenia Research*, *131*(1–3), 133–138. https://doi.org/10.1016/j.schres.2011.05.023
50. Saifaddin, D. L., Mohammed, S. S., Rahim, H. A., Ghanbari, N., Kareem, D. A., Abdollah, H. H., & Omar, S. M. (2023). Endurance training and L-arginine intake: Their effect on antioxidant indices in the heart muscles of rats. *Nutrition and Health*. https://doi.org/10.1177/02601060231187514
51. Sakurai, T., Kashimura, O., Kano, Y., Ohno, H., Ji, L. L., Izawa, T., & Best, T. M. (2013). Role of nitric oxide in muscle regeneration following eccentric muscle contractions in rat skeletal muscle. *The Journal of Physiological Sciences*, *63*(4), 263–270. https://doi.org/10.1007/s12576-013-0262-y
52. Schwedhelm, E., Maas, R., Freese, R., Jung, D., Lukacs, Z., Jambrecina, A., Spickler, W., Schulze, F., & Böger, R. H. (2007). Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism.

British Journal of Clinical Pharmacology, *65*(1), 51–59. https://doi.org/10.1111/j.1365-2125.2007.02990.x

53. Shao, A., & Hathcock, J. N. (2008). Risk assessment for the amino acids taurine, l-glutamine and l-arginine. *Regulatory Toxicology and Pharmacology*, *50*(3), 376–399. https://doi.org/10.1016/j.yrtph.2008.01.004
54. Shashar, M., Hod, T., Chernichovski, T., Angel, A., Kazan, S., Grupper, A., Naveh, S., Bassat, O. K., Weinstein, T., & Schwartz, I. F. (2018). Mineralocorticoid receptor blockade improves arginine transport and nitric oxide generation through modulation of cationic amino acid transporter-1 in endothelial cells. *Nitric Oxide*, *80*, 24–31. https://doi.org/10.1016/j.niox.2018.07.007
55. Shen, S., & Hua, C. (2010). Effect ofL-arginine on the expression of Bcl-2 and Bax in the placenta of fetal growth restriction. *The Journal of Maternal-Fetal & Neonatal Medicine*, *24*(6), 822–826. https://doi.org/10.3109/14767058.2010.531315
56. Šimko, F., Potáčová, A., Pelouch, V., Paulis, L., Matuskova, J., Krajčirovičová, K., Pecháňová, O., & Adamcová, M. (2007). Spontaneous, L-Arginine-Induced and Spironolactone-Induced regression of protein remodeling of the left ventricle in L-NAME-Induced hypertension. *Physiological Research*, S55–S62. https://doi.org/10.33549/physiolres.931398
57. Speer, H., D'Cunha, N. M., Davies, M. J., McKune, A. J., & Naumovski, N. (2020). The physiological effects of amino acids arginine and citrulline: Is there a basis for development of a beverage to promote endurance performance? A narrative review of orally administered supplements. *Beverages*, *6*(1), 11. https://doi.org/10.3390/beverages6010011
58. Šušnjara, P., Mihaljević, Z., Stupin, A., Kolobarić, N., Matić, A., Jukić, I., Kralik, Z., Kralik, G., Miloloža, A., Pavošević, T., Šerić, V., Lončarić, Z., Kerovec, D., Galović, O., & Drenjančević, I. (2023). Consumption of nutritionally enriched hen eggs enhances Endothelium-Dependent vasodilation via cyclooxygenase metabolites in healthy young People—A randomized study. *Nutrients*, *15*(7), 1599. https://doi.org/10.3390/nu15071599
59. Tan, B. (2015). L-Arginine improves DNA synthesis in LPS-challenged enterocytes. *Frontiers in Bioscience*, *20*(6), 989–1003. https://doi.org/10.2741/4352
60. Tripathi, P., Chandra, M., & Misra, M. K. (2009). Oral administration of L-Arginine in patients with angina or following myocardial infarction may be protective by

increasing plasma superoxide dismutase and total thiols with reduction in serum cholesterol and xanthine oxidase. *Oxidative Medicine and Cellular Longevity*, *2*(4), 231–237. https://doi.org/10.4161/oxim.2.4.9233

61. Trofimova, E. S., Zykova, M. V., Danilets, M. G., Ligacheva, A. A., Sherstoboev, E. Y., Selivanova, N. S., Azarkina, L. A., Zhirkova, A. M., Zhang, Y., Perminova, I. V., Zhdanov, V. V., & Belousov, M. V. (2024). Effect of modified forms of sodium humate POWHUMUS on the balance of arginine in peritoneal macrophages of intact mice. *Bulletin of Experimental Biology and Medicine*, *177*(1), 68–73. https://doi.org/10.1007/s10517-024-06133-9
62. Viribay, A., Burgos, J., Fernández-Landa, J., Seco-Calvo, J., & Mielgo-Ayuso, J. (2020a). Effects of arginine Supplementation on Athletic Performance Based on Energy Metabolism: A Systematic Review and Meta-Analysis. *Nutrients*, *12*(5), 1300. https://doi.org/10.3390/nu12051300
63. Viribay, A., Burgos, J., Fernández-Landa, J., Seco-Calvo, J., & Mielgo-Ayuso, J. (2020b). Effects of arginine Supplementation on Athletic Performance Based on Energy Metabolism: A Systematic Review and Meta-Analysis. *Nutrients*, *12*(5), 1300. https://doi.org/10.3390/nu12051300
64. Viribay, A., Burgos, J., Fernández-Landa, J., Seco-Calvo, J., & Mielgo-Ayuso, J. (2020c). Effects of arginine Supplementation on Athletic Performance Based on Energy Metabolism: A Systematic Review and Meta-Analysis. *Nutrients*, *12*(5), 1300. https://doi.org/10.3390/nu12051300
65. Wang, R., Jiao, H., Zhao, J., Wang, X., & Lin, H. (2018a). L-Arginine enhances protein synthesis by phosphorylating MTOR (THR 2446) in a nitric Oxide-Dependent manner in C2C12 cells. *Oxidative Medicine and Cellular Longevity*, *2018*, 1–13. https://doi.org/10.1155/2018/7569127
66. Wang, R., Jiao, H., Zhao, J., Wang, X., & Lin, H. (2018b). L-Arginine enhances protein synthesis by phosphorylating MTOR (THR 2446) in a nitric Oxide-Dependent manner in C2C12 cells. *Oxidative Medicine and Cellular Longevity*, *2018*, 1–13. https://doi.org/10.1155/2018/7569127
67. Willoughby, D. S. (2015). INTRACELLULAR MECHANISTIC ROLE OF NITRIC OXIDE: A COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF L-ARGININE AND L-CITRULLINE SUPPLEMENTATION ON NITRIC OXIDE SYNTHESIS AND SUBSEQUENT EXERCISE PERFORMANCE IN HUMANS.

International Journal of Food and Nutritional Science, *2*(1), 1–8. https://doi.org/10.15436/2377-0619.15.010

68. Wu, G., Bazer, F. W., Davis, T. A., Kim, S. W., Li, P., Rhoads, J. M., Satterfield, M. C., Smith, S. B., Spencer, T. E., & Yin, Y. (2008). Arginine metabolism and nutrition in growth, health and disease. *Amino Acids*, *37*(1), 153–168. https://doi.org/10.1007/s00726-008-0210-y
69. Wu, G., Meininger, C. J., McNeal, C. J., Bazer, F. W., & Rhoads, J. M. (2021). Role of L-Arginine in nitric oxide synthesis and health in humans. In *Advances in experimental medicine and biology* (pp. 167–187). https://doi.org/10.1007/978-3-030-74180-8_10
70. Wu, G., & Morris, S. M. (1998). Arginine metabolism: nitric oxide and beyond. *Biochemical Journal*, *336*(1), 1–17. https://doi.org/10.1042/bj3360001
71. Yaman, H., Sönmez, G. T., & Gürel, K. (2010). Effects of oral L-arginine supplementation on vasodilation and O2max in male soccer players. *Biomedical Human Kinetics*, *2*(2010), 25–29. https://doi.org/10.2478/v10101-010-0006-x
72. Yuan, C., Ding, Y., He, Q., Azzam, M., Lu, J., & Zou, X. (2015). L-arginine upregulates the gene expression of target of rapamycin signaling pathway and stimulates protein synthesis in chicken intestinal epithelial cells. *Poultry Science*, *94*(5), 1043–1051. https://doi.org/10.3382/ps/pev051
73. Zheng, X., Liu, T., Chen, X., Chen, X., Jiang, J., & Hu, P. (2015). Investigation of a potential pharmacokinetic interaction between perindopril arginine and amlodipine when administered as a single perindopril/amlodipine fixed-dose combination tablet in healthy Chinese male volunteers. *International Journal of Clinical Pharmacology and Therapeutics*, *54*(01), 43–51. https://doi.org/10.5414/cp202250
74. Zhou, Y., Liu, G., Huang, H., & Wu, J. (2021). Advances and impact of arginine-based materials in wound healing. *Journal of Materials Chemistry B*, *9*(34), 6738–6750. https://doi.org/10.1039/d1tb00958c