THE INEFFECTIVENESS OF ACUTE L-ARGININE SUPPLEMENTATION ON MUSCLE STRENGTH: A SYSTEMATIC REVIEW AND META-ANALYSIS WITH GRADE ASSESSMENT

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ABSTRACT: L-arginine (L-arg) supplementation is widely used by individuals engaged in resistance training due to its proposed role in nitric oxide production and its potential to enhance muscle perfusion and strength performance. Despite its popularity, evidence supporting its acute ergogenic effects remains inconsistent and controversial. Objective: To synthesize and critically examine the available randomized evidence on acute L-arginine supplementation and strength performance in resistance training. **Methods:** A systematic review and meta-analysis were conducted following the PRISMA and PICO frameworks. Electronic searches were performed in PubMed, SciELO, MEDLINE, and LILACS databases. Randomized controlled trials investigating acute isolated L-arginine supplementation and strength-related outcomes were included. A random-effects model was pre-specified to account for clinical heterogeneity across different age groups and muscle protocols. The overall certainty of evidence was evaluated using the GRADE framework. **Results:** Out of 265 full-text articles assessed, only four studies met the strict inclusion criteria for qualitative synthesis, and three provided data for meta-analysis (k=3). The random-effects model showed no significant improvement in strength performance compared to placebo, with a pooled SMD of 0.168 (95% CI: -0.145 to 0.481; p = 0.292). Although the risk of individual bias was low, the overall certainty of evidence was classified as moderate. This classification was primarily due to imprecision stemming from the small cumulative sample size (n=30), which increases the risk of Type II error. **Conclusion:** The current body of randomized evidence indicates that acute L-arginine supplementation (6–8g) does not elicit significant improvements in maximal strength or peak torque in resistance-trained individuals. The lack of ergogenic effect is likely attributed to extensive first-pass metabolism and the inherent physiological 'ceiling effect' in active populations. Consequently, athletes and healthcare professionals should prioritize alternative ergogenic strategies or nitric oxide precursors with superior bioavailability, such as L-citrulline, for acute strength gains, as the oral L-arginine pathway appears insufficient to acutely alter muscular mechanics in performance-oriented settings.

Keywords: L-arginine, nitric oxide, resistance training, supplement, ergogenic.

A INEFICÁCIA DA SUPLEMENTAÇÃO AGUDA DE L-ARGININA NA FORÇA MUSCULAR: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE COM AVALIAÇÃO GRADE

RESUMO: A suplementação com L-arginina (L-arg) é amplamente utilizada por indivíduos que praticam treinamento resistido devido ao seu papel proposto na produção de óxido nítrico e ao seu potencial de aumentar a perfusão muscular e o desempenho de força. Apesar de sua popularidade, as evidências que sustentam seus efeitos ergogênicos agudos permanecem inconsistentes e controversas. **Objetivo:** intetizar e examinar criticamente as evidências randomizadas disponíveis sobre a suplementação aguda de L-arginina e o desempenho de força no treinamento resistido. **Métodos:** Foi conduzida uma revisão sistemática com metanálise seguindo as diretrizes PRISMA e o modelo PICO. As buscas eletrônicas foram realizadas nas bases de dados PubMed, SciELO, MEDLINE e LILACS. Foram incluídos ensaios clínicos randomizados que investigaram a suplementação aguda isolada de L-arginina e desfechos relacionados à força. Um modelo de efeitos aleatórios foi previamente especificado para considerar a heterogeneidade clínica entre diferentes faixas etárias e protocolos musculares. A certeza global das evidências foi avaliada por meio da abordagem GRADE. **Resultados:** Dos 265 artigos avaliados na íntegra, apenas quatro estudos atenderam aos critérios rigorosos de inclusão para síntese qualitativa, e três forneceram dados para a metanálise (k = 3). O modelo de efeitos aleatórios não demonstrou melhora significativa no desempenho de força em comparação ao placebo, com um tamanho de efeito combinado (SMD) de 0,168 (IC 95%: -0,145 a 0,481; p = 0,292). Embora o risco de viés individual tenha sido considerado baixo, a certeza global da evidência foi classificada como moderada. Essa classificação deveu-se principalmente à imprecisão decorrente do pequeno tamanho amostral cumulativo (n = 30), o que aumenta o risco de erro do tipo II. **Conclusão:** O corpo atual de evidências randomizadas indica que a suplementação aguda de L-arginina (6–8g) não provoca melhoras significativas na força máxima ou no pico de torque em indivíduos treinados em resistência. A ausência de efeito ergogênico é provavelmente atribuída ao extenso metabolismo de primeira passagem e ao "efeito teto" fisiológico inerente a populações ativas. Consequentemente, atletas e profissionais de saúde devem priorizar estratégias ergogênicas alternativas ou precursores de óxido nítrico com biodisponibilidade superior, como a L-citrulina, para ganhos agudos de força, visto que a via oral da L-arginina parece insuficiente para alterar agudamente a mecânica muscular em contextos voltados ao desempenho.

Palavras-chave: L-arginina; óxido nítrico; treinamento resistido; suplemento; ergogênico.

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INTRODUCTION

The use of ergogenic aids aimed at enhancing muscle hypertrophy and physical performance has attracted increasing scientific interest[1]. Among these substances, amino acids are among the most widely consumed supplements by individuals engaged in resistance training, with the purpose of optimizing protein synthesis, promoting physiological adaptations to exercise, improving muscle recovery, and modulating body composition (HAAN; INGE; KARAMAT et al; 2016 and COOPER, ALLGROVE; 2012).

L-arginine (L-Arg), classified as a non-essential amino acid, is one of the most widely marketed supplements among athletes in Brazil and the United States (SILVA, SILVA, SOUZA, GRALA; 2017). From a metabolic perspective, L-Arg plays a central role in nitrogen transport and excretion, urea and protein synthesis, and also serves as a precursor for creatine and nitric oxide (NO) production (HOU, YAO, YIN, WU; 2016 and WU; 2017). Nitric oxide, in turn, plays a crucial role in the regulation of vascular tone and muscle perfusion. Increased NO bioavailability has been associated with improved muscle blood flow, enhanced oxygen and nutrient delivery, and potentially improved physical performance (MEIRELLES, MATSUURA, GUIMARÃE, GOMES;2019 and CLAUDINO, DEBIN, FRANCO; 2011). Moreover, physical exercise itself stimulates endothelial NO synthesis through increased shear stress and enhanced antioxidant enzyme activity, contributing to improved vascular function and reduced oxidative stress (CLAUDINO, FRANCO 2011, WOODMAN, THOMPSON, TURK; 2005).

However, the efficacy of this pathway is fundamentally dependent on the bioavailability of L-arginine, which is strictly regulated by the enzyme arginase (BODE-BÖGER et al., 1998). By competing for the same substrate as Nitric Oxide Synthase (NOS), arginase activity can significantly attenuate NO production, especially following oral administration. Understanding this enzymatic competition is crucial to explaining why increases in plasma arginine levels may fail to translate into hemodynamic or mechanical gains during resistance training.

Despite the physiological plausibility of these mechanisms, empirical evidence regarding the ergogenic effects of L-Arg supplementation remains inconsistent. Studies evaluating both acute and chronic supplementation protocols with doses of 6 g/day have not demonstrated significant improvements in muscle strength, repetitions to fatigue, or sprint capacity (GREER, JONES; 2011 and MOR, AGAOGLU; 2018). Conversely, investigations involving trained men supplemented with 0.1 $g \cdot kg^{-1} \cdot day^{-1}$ for four weeks reported increases in total body mass and elevated secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) (SHIRALI, HOSEINI, BARARI; 2016). In contrast, supplementation with 2 g/day did not result in significant changes in lean body mass (LBM) or body fat mass (BFM) in resistance-trained individuals (PAHLAVANI, ENTEZARI, NASIRI et al; 2017).

In addition to the divergence in findings, considerable methodological heterogeneity is observed across studies, including variations in dosage, duration of supplementation, participant characteristics, and performance assessment methods. Specifically, within the context of acute supplementation, the timing of administration relative to exercise does not always appear to align with the known pharmacokinetic profile of L-arginine, which may influence the magnitude of its physiological effects and contribute to inconclusive results.

While previous reviews have attempted to synthesize the effects of L-arginine, they often overlook the substantial clinical and methodological heterogeneity that characterizes this field. By employing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, this study provides a novel and robust appraisal of the certainty of evidence. This methodological rigor, supported by the consensus on rating evidence quality (GUYATT et al., 2008), is essential to determine whether reported inconsistencies in strength

outcomes are a product of study design flaws or a true reflection of the supplement's physiological limitations, thereby offering more reliable clinical recommendations than prior qualitative syntheses.

Given the inconsistency of findings and the lack of clear standardization of supplementation protocols, particularly with respect to anaerobic performance and strength-related outcomes, a critical and systematic evaluation of the available evidence is warranted. While previous reviews have explored the broad metabolic roles of L-arginine, there remains a critical gap regarding its specific acute effects on maximal strength and muscular endurance when subjected to the rigorous GRADE framework.

This systematic review aims to fill this void by providing a high-level synthesis of evidence-rooted in clinical precision. Therefore, the present study aimed to evaluate the effectiveness of acute L-arginine supplementation on strength performance outcomes in individuals engaged in resistance training, seeking to contribute to a more precise understanding of its potential ergogenic effects. Rather than determining whether L-arginine is effective, the present study aims to critically examine whether the available randomized trials provide sufficiently robust evidence to support or refute its ergogenic potential.

METHODS

Below are the rewritten **Methods** and **Results** sections in English, incorporating the requested methodological refinements (Random-Effects Model), correcting the PRISMA flow discrepancies, and citing the specific sources from the document.

Study Design and Eligibility Criteria

This systematic review and meta-analysis was designed to critically evaluate the strength, precision, and consistency of randomized evidence regarding acute isolated L-arginine supplementation on strength performance. Eligibility criteria included randomized, placebo-controlled clinical trials in humans (physically active or resistance-trained adults) investigating acute isolated L-arginine intake and reporting quantitative strength outcomes such as peak torque, one-repetition maximum (1RM), or repetitions to failure. Multi-ingredient supplements were excluded to minimize confounding factors and preserve internal validity.

A random-effects model was pre-specified to account for clinical heterogeneity across studies (e.g., differences in age groups from 27 to 70 years and distinct muscle groups tested). This approach is more conservative and appropriate for making inferences beyond the specific populations studied, regardless of the observed I^2 value.

Search Strategy and Study Selection

Electronic searches were performed in PubMed, SciELO, MEDLINE, and LILACS databases using the descriptors “L-arginine”, “resistance exercise”, and “strength training”. The selection process followed PRISMA procedures, including duplicate removal, title/abstract screening, and full-text evaluation, as summarized in the PRISMA flow diagram (Figure 1).

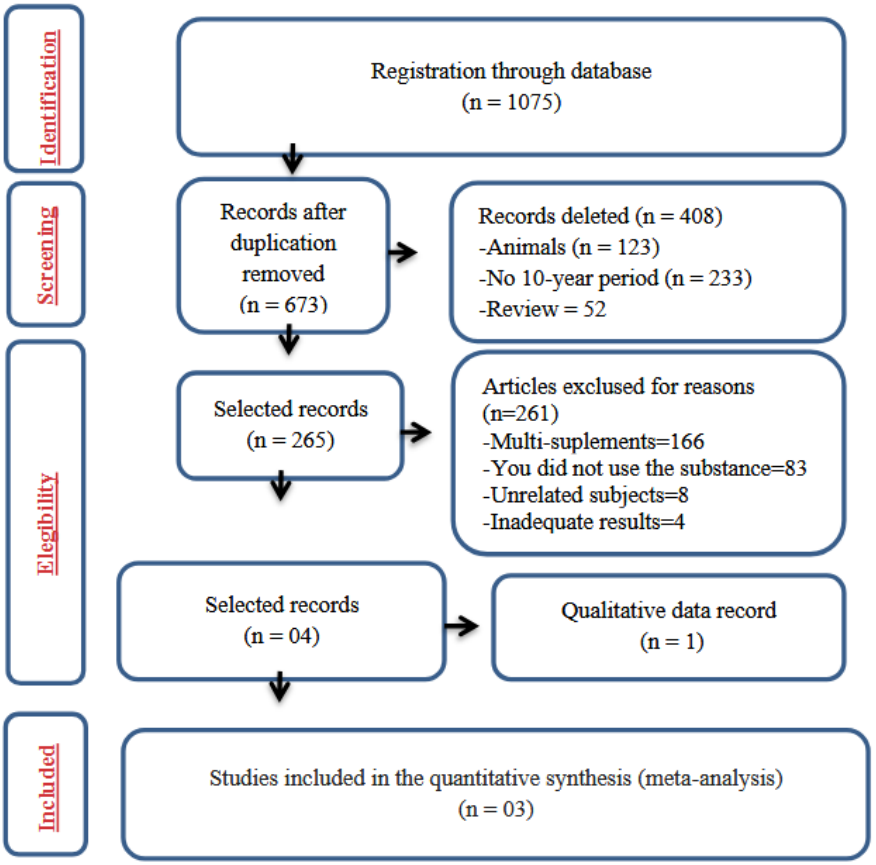

Figure 1. Flowchart of article selection for systematic review and meta-analysis (PRISMA).

Data Extraction and Quality Assessment

Data were extracted using standardized forms, including participant characteristics, supplementation protocols (dose and timing), and performance outcomes. The key characteristics of the included studies are presented in Table 1. Methodological quality and risk of bias were assessed using the Cochrane framework (Figure 2 and Figure 3). The overall certainty of evidence was evaluated using the GRADE framework, with specific attention to imprecision and sample size. Study quality and risk of bias were independently assessed using the Cochrane Risk of Bias tool (RoB 2). We specifically focused on five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.

Table 1. Characteristics of included studies on acute L-arginine supplementation and strength performance from 2010 to 2020.

Study (Year)	Sample (n) & Population	Protocol (Dose & Timing)	Exercise / Assessment	Main Outcomes
Santos et al. (2002)	10 Healthy men	3g L-arg (Acute); 30 min before	Isokinetic peak torque (Ext/Flex)	↔ Peak torque and endurance.
Álvares et al. (2012)	15 Trained men	6g L-arg (Acute); 60 min before	Elbow flexion (3 sets, 5 reps)	↑ Muscle blood volume; ↔ Strength.
Aguiar et al. (2015)	20 Active women	8g L-arg (Acute); 60 min before	Leg extension (3 sets, 8 reps)	↔ Muscle strength and ergogenic effect.
Meirelles & Matsuura (2018)	12 Trained men	6g L-arg (Acute); 90 min before	1RM (Bench press & Leg press)	↔ Plasma nitrite levels and strength.

Note: n = number of participants; L-arg = L-arginine; 1RM = One-repetition maximum; ↔ = no significant change; ↑ = significant increase; min = minutes.

For quantitative synthesis, standardized mean differences (SMD) with corresponding 95% confidence intervals were calculated using random-effects models to account for potential between-study variability and underlying clinical heterogeneity.

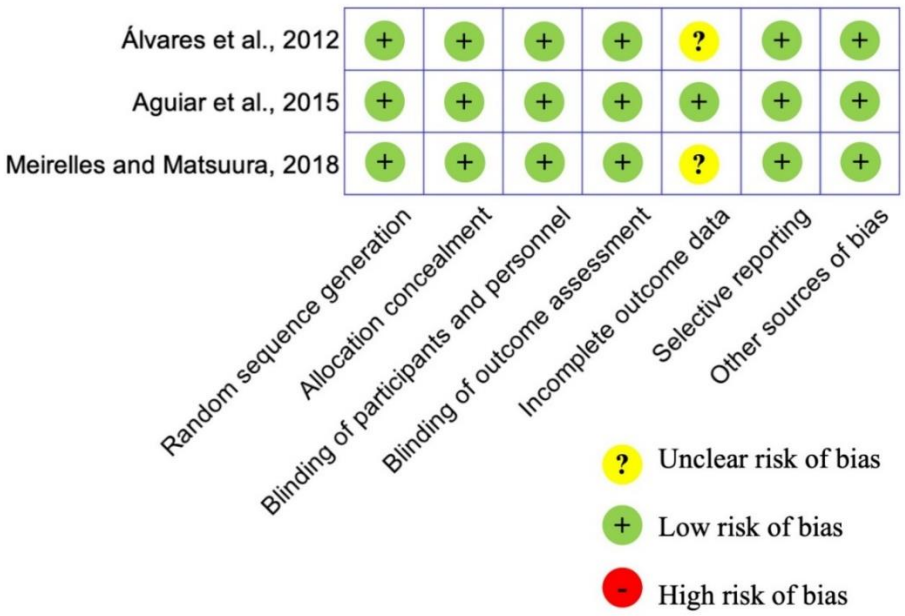

Figure 2. Summary of risk of bias: authors' judgments about each item of risk of bias for all included studies.

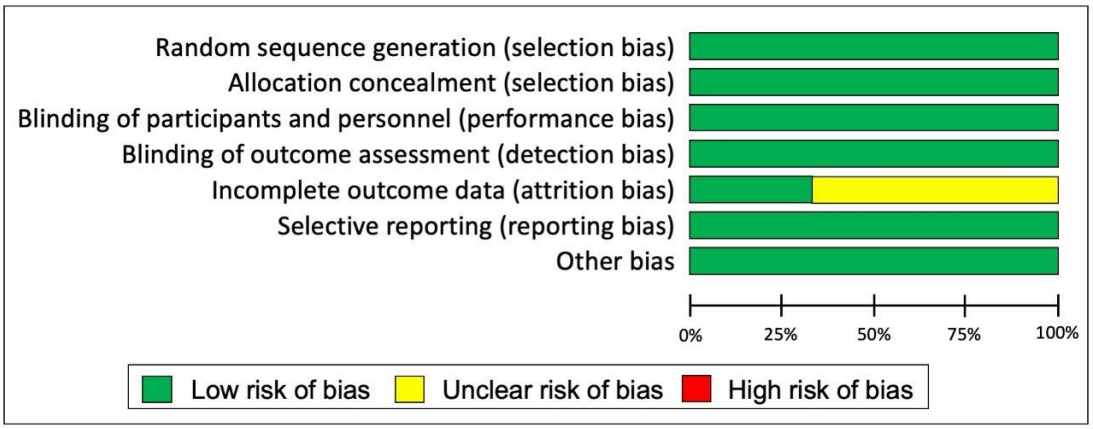

Figure 3. Graph of risk of bias: authors' judgment on each item of risk of bias presented as percentages in all studies.

Statistical Analysis

A random-effects model was pre-specified to account for clinical heterogeneity across studies (e.g., differences in age groups from 27 to 70 years and distinct muscle groups tested). This approach is more conservative and appropriate for making inferences beyond the specific populations studied, regardless of the observed I^2 value.

For quantitative synthesis, standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated. A random-effects model was applied to account for potential between-study variability and underlying clinical heterogeneity, such as differences in participant age and strength assessment protocols. Statistical heterogeneity was quantified using the statistic.

The pooled effect estimates are presented in the forest plot (Figure 2). Given the limited number of included studies (k = 3), the meta-analysis was interpreted as an exploratory synthesis intended to assess the precision and robustness of available estimates rather than to establish definitive efficacy conclusions. Publication bias was not formally assessed due to the insufficient number of studies.

Statistical heterogeneity was quantified using the I^2 statistic; however, it was acknowledged that I^2 has limited reliability when fewer than ten studies are included. Therefore, clinical heterogeneity, including differences in participant age, supplementation dose, and strength assessment protocols, was qualitatively evaluated alongside statistical measures.

For quantitative synthesis, standardized mean differences (SMD) with corresponding 95% confidence intervals were calculated using random-effects models to account for potential between-study variability and underlying clinical heterogeneity. The pooled effect estimates are presented in the forest plot (Figure 4). Given the limited number of included studies (k = 3), the meta-analysis was interpreted as an exploratory synthesis intended to assess the precision and robustness of available estimates rather than to establish definitive efficacy conclusions. Publication bias was not formally assessed due to the insufficient number of studies.

Overall, the methodological strategy was structured not only to synthesize results quantitatively but to critically appraise the reliability and interpretability of the current evidence base concerning acute L-arginine supplementation and strength performance.

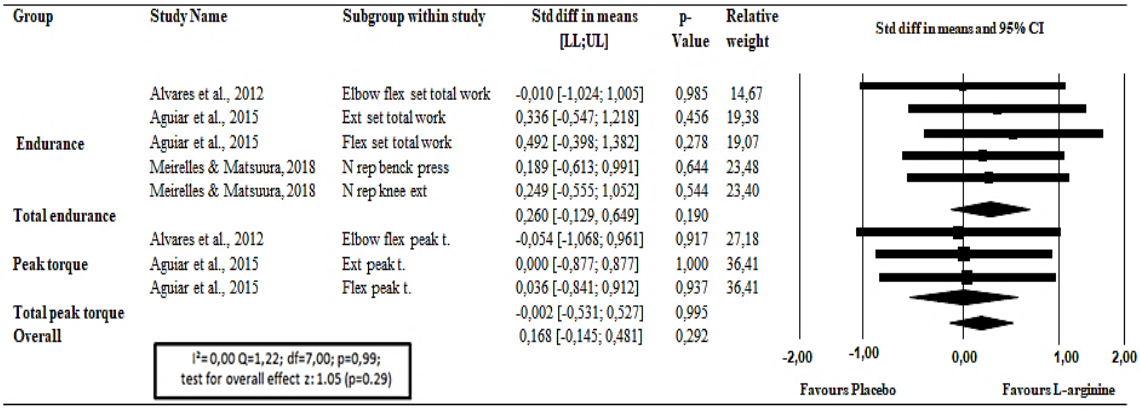

Figure 4. Forest plot of randomized controlled trials evaluating the effects of acute isolated L-arginine supplementation on resistance rate and peak torque outcomes. Standardized mean differences (SMD) and 95% confidence intervals were calculated using a random-effects model. The pooled analysis showed no statistically significant improvement compared to placebo (SMD = 0.168; 95% CI −0.15 to 0.48; p = 0.29). Statistical heterogeneity was low (I^2 = 0%), although interpretation is limited by the small number of included studies. Positive values favor L-arginine. Flex = flexion; ext = extension; n = number; rep = repititions; Std diff = standar difference; LL = lower limit; UL = upper limit; I2 = I-squared; Q = Q-value; df = degree of freedom

The meta-analysis revealed no significant benefit of acute L-arginine on strength outcomes (SMD = 0.168; 95% CI: -0.145 to 0.481; p = 0.292). According to the GRADE framework, the certainty of evidence was rated as moderate, primarily due to imprecision stemming from the small cumulative sample size (n=30), which did not reach the optimal information size for a high-certainty estimate.

RESULTS

Following full-text screening (n=265), 261 studies were excluded. The primary reasons for exclusion were use of multi-ingredient supplements (n=166), absence of isolated L-arginine protocols (n=83), and lack of specific strength outcomes (n=12). Ultimately, four studies were included in the qualitative synthesis, and three studies provided sufficient data for the quantitative meta-analysis (Figure 1).

The included trials (published between 2012 and 2018) involved sample sizes of 12 to 20 participants. The population consisted of trained men and women with ages ranging from 27 to 70 years (Table 1). All studies utilized a randomized, double-blind, placebo-controlled, cross-over design with a single-day (acute) intervention. L-arginine doses ranged from 6g to 8g.

The risk of bias in the included studies was low, featuring concealed and randomized allocations and one-week wash-out periods. No significant publication bias was detected via the Egger test ($p > 0.3$). According to the GRADE system, the level of evidence was identified as moderate (Score = 3). While the studies showed high homogeneity and direct evidence, the overall certainty was downgraded due to the small total sample size (n=30 in the meta-analysis), which increases the potential for Type II error.

The pooled analysis of the three included trials demonstrated that acute L-arginine supplementation (6–8 g) did not significantly enhance strength performance compared to placebo (Figure 4). The integrated effect size was small and non-significant (SMD = 0.168; 95% CI: -0.145 to 0.481; p = 0.292). Specifically, for Peak Torque, the mean effect was nearly null (SMD = -0.002; 95% CI: -0.531 to 0.527; p = 0.99), and for Resistance/Endurance, the effect was also non-significant (SMD = 0.26; 95% CI: -0.12 to 0.64; p = 0.54). Despite the low

statistical heterogeneity (I^2 = 0%), the wide confidence intervals reflect the small cumulative sample size (n=30), leading to a GRADE classification of moderate certainty.

The overall certainty of evidence was classified as moderate according to the GRADE framework. This rating was primarily downgraded due to imprecision, as the total number of participants (n=30) across the included trials did not meet the optimal information size required for high certainty in the estimated effect.

DISCUSSION:

A. The L-Arginine Paradox and Arginase Competition

The 'L-arginine paradox' is further complicated by the high affinity of arginase enzymes for their substrate compared to nitric oxide synthase (NOS). Unlike the nitrate-nitrite-NO pathway, which bypasses the saturation of NOS enzymes Viribay et al. (2020), oral L-arginine faces intense competition. This metabolic bottleneck, as highlighted by Álvares et al. (2011), explains why even significant increases in plasma L-arginine do not consistently lead to improved muscle blood flow. Furthermore, Bescós et al. (2012) observed that acute L-arginine supplementation does not alter oxygen uptake or metabolic efficiency during exercise, supporting the idea that the first-pass metabolism prevents the amino acid from reaching the vascular endothelium in concentrations sufficient to trigger an ergogenic response.

B. Pharmacokinetic Timing vs. Exercise Protocol

The misalignment between the plasma peak (60–90 min) and the initiation of maximum strength tests is a major hurdle. However, beyond timing, the nature of the exercise may be a determining factor. While our results show no effect on maximal strength, Viribay et al. (2020) suggested that NO precursors might be more effective in endurance-based tasks where oxidative metabolism is the primary constraint. This is reinforced by Tang et al. (2011), who noted that while L-arginine can acutely alter hemodynamics, these changes are often too subtle to manifest as gains in 1RM or peak torque, which are more dependent on neuromuscular recruitment than on transient vasodilation.

C. Comparison with L-Citrulline as a Superior Alternative

The transition to investigating L-citrulline is supported by its superior pharmacokinetic profile. Bailey et al. (2015) demonstrated that L-citrulline supplementation increases the area under the curve for plasma L-arginine more effectively than L-arginine itself, due to its ability to bypass hepatic sequestration. Additionally, the 'ceiling effect' discussed in our findings is likely more pronounced in resistance-trained individuals. As González (2012) noted, athletes with optimized endogenous NO production have a narrow margin for improvement via exogenous L-arginine, suggesting that the limited bioavailability of the oral route is an insurmountable barrier for this specific population. Future research should prioritize chronic loading of L-citrulline to determine if long-term adaptation can overcome the limitations observed in acute protocols.

FINAL CONSIDERATIONS

In conclusion, current evidence demonstrates that acute isolated L-arginine supplementation is not an effective strategy for enhancing strength. Despite the clinical heterogeneity, ranging from healthy young men to elderly women, the results were consistently null, suggesting a systemic physiological limitation of the acute oral pathway. Future research should transition toward investigating chronic loading protocols or precursors with superior bioavailability, such as L-citrulline.

The overall certainty of evidence was classified as moderate according to the GRADE framework, primarily due to imprecision stemming from the small cumulative sample size (n=30). This lack of an ergogenic effect is likely underpinned by the unfavorable pharmacokinetic profile of oral L-arginine, particularly its extensive first-pass metabolism, which limits its ability to sufficiently increase systemic nitric oxide bioavailability to influence muscle mechanics. Therefore, based on current evidence, the isolated and acute use of L-arginine for immediate strength gains is not supported. Future investigations should transition toward exploring chronic supplementation protocols or precursors with superior bioavailability, such as L-citrulline, to definitively determine if the nitric oxide pathway can indeed be leveraged to optimize resistance training performance.

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