# L-Arginine™

## Clinical Benefits

- **Improves endothelial function; most effective in flow-impaired vessels***
- **Restores nitric oxide levels, supporting blood vessel & cardiovascular health***
- **Helps maintain optimal blood pressure***
- **Antioxidant effect independent of nitric oxide production***
- **Vital for wound healing, fertility, immune function, collagen & hydroxyproline production***
- **Supports adipose tissue metabolism***


**L-Arginine**
available in a
100 capsule
bottle (#5102)

## Nitric Oxide & Endothelial Function

L-Arginine, a conditionally essential amino acid, is the rate-limiting substrate for the enzymes nitric oxide synthase (NOS) and arginase, and is necessary for the production of nitric oxide and urea, respectively. Of the two pathways which require L-arginine, the most well-known is the biosynthesis of nitric oxide, given the critical role of nitric oxide production in maintaining healthy endothelial function and vascular homeostasis. Nitric oxide relaxes vascular smooth muscle, inhibits platelet aggregation and adhesion, and also limits the ability of leukocytes to adhere to the vascular wall through multiple mechanisms. Endothelial dysfunction caused by a reduction in nitric oxide leads to not only a less-compliant blood vessel wall, but also a more prothrombotic and proinflammatory one.[1] Reduced production or sensitivity of nitric oxide in the endothelium is central to this dysfunction, and underlies many cardiovascular diseases, including hypertension, atherosclerosis, and diabetes, as well as age-related cognitive decline, and both renal and erectile dysfunction.[2,3]

Many of these same conditions are associated with elevated levels of asymmetric dimethylarginine (ADMA), a competitor with L-arginine for both NOS binding as well as for transport into the endothelial cell. ADMA inhibits the synthesis of nitric oxide by competing with L-arginine, and thus elevated levels of ADMA, especially relative to L-arginine, are an independent predictor of cardiovascular risk.[4,5] While ADMA alone has been found to predict both all-cause and cardiovascular mortality in patients with coronary artery disease, the ratio of L-arginine to ADMA provides a better window into the availability of nitric oxide for NOS, and thus may be a better predictor of cardiovascular risk.[6,7] Supplementation with L-arginine boosts its cellular availability and increases the production of nitric oxide, and has been associated with clinically significant reductions in both systolic and diastolic blood pressure.[8]

In a meta-analysis of controlled trials, L-arginine was also found to increase flow-mediated dilation, with an effect inversely related to baseline flow. The findings of this meta-analysis indicate that the lower the baseline flow, i.e., the greater degree of endothelial dysfunction, the greater the effect L-arginine has on improving flow. In other words, L-arginine supplementation improves endothelial function, but does not further enhance flow in an already healthy blood vessel.[9] Supplementation has also been shown to prevent the increase in blood pressure following exposure to traffic-related air pollution among people with hypertension, a common trigger for spikes in blood pressure.[10]

## Cardiovascular Fitness & Antioxidant Effects

Improved blood flow may also explain associated gains in cardiovascular fitness, as supplementation has been associated with improved maximal oxygen uptake, i.e., VO2max, as well as gains in aerobic and anaerobic performance.[11,12] Additionally, randomized and controlled trials have shown an antioxidant effect of L-arginine supplementation independent of nitric oxide formation, which may help to mitigate the oxidative stress associated with endothelial dysfunction.[13,14] Indeed, oxidative stress may be the primary trigger for an increase in ADMA levels, at least in response to postprandial hyperglycemia.[15] In a trial among prediabetics, a lower conversion to diabetes following L-arginine supplementation over a long period was attributed to this reduction in oxidative stress.[16] ADMA levels have also been found to be elevated among patients with obstructive sleep apnea, and may be predictive of risk.[17]

BIOTICS® RESEARCH CORPORATION

**(905)476-3554**
Biotics Researc Canada
Box 283 Keswick On L4P 3E2
orders@bioticscan.com

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.


LIT-353 Rev. 02/22

## Urea Cycle, Wound Healing & Immune Function

In addition to its role as a precursor for nitric oxide, L-arginine also participates in the urea cycle as a substrate for the enzyme arginase. The urea cycle is needed both for the elimination of ammonia, as well as the synthesis of ornithine, which is itself the substrate for polyamines and proline. While proline is needed for collagen formation, polyamines (including putrescine, spermidine and spermine) regulate multiple cellular processes, ranging from DNA replication, gene expression, and protein translation to wound healing, tissue repair, fertility and immune function, suggesting several related clinical uses of L-arginine.[18] L-arginine supplementation has been shown to promote wound healing, for example, in part mediated by an increase in collagen and hydroxyproline deposition, which translates into better wound healing in older adults in both acute and long-term care settings.[19,20] L-arginine influences the biology of multiple immune cells, including macrophages, dendritic, B and T cells, and has also been used clinically to support immune function; in one randomized clinical trial, older adults supplemented with L-arginine had improved neutrophil chemotaxis, natural killer cytotoxicity and IgG production compared to placebo, following vaccination against Streptococcus pneumoniae.[21,22]

## Arginase & Adipose Metabolism

Because L-arginine is a substrate for both nitric oxide synthase and arginase, there may also be a limited amount of arginine available if either of these enzymes is overexpressed. For example, elevated arginase expression has been found in a number of chronic conditions and is thought to reduce the amount of L-arginine available for nitric oxide synthase. Obesity, for example, has been associated with an upregulation of arginase, a reduction in nitric oxide synthase activity, and increased oxidative damage (via NOS uncoupling) as a consequence. Multiple animal models suggest that this increase in arginase activity may in part underlie many of the metabolic abnormalities associated with obesity, including endothelial dysfunction, hypertension, visceral adipose tissue inflammation, and insulin resistance. Nitric oxide appears to not only influence vascular function, but adipose metabolism as well.[23] That L-arginine supplementation may positively influence adipose tissue function was supported by a systematic review of clinical trials, which found a reduction in waist circumference following L-arginine supplementation, with subgroup analysis indicating a reduction in body mass index with a longer duration of supplementation.[24] Additionally, meta-analysis results suggest L-arginine may have an influence on lipid and/or glucose metabolism, as supplementation has been associated with a significant reduction in triglyceride levels.[25] The evidence base continues to grow for the role of nitric oxide and L-arginine in regulating a wide variety of metabolic and immune pathways, far beyond the physiology of vasodilation.

### References


1. Cyr AR, Huckaby LV, Shiva SS, et al. Nitric Oxide and Endothelial Dysfunction. *Crit Care Clin.* 2020 Apr;36(2):307-321.
2. Gambardella J, Khondkar W, Morelli MB, et al. Arginine and Endothelial Function. *Biomedicines.* 2020 Aug 6;8(8):277.
3. Gimbrone MA Jr, García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res.* 2016 Feb 19;118(4):620-36.
4. Notsu Y, Yano S, Shibata H, et al. Plasma arginine/ADMA ratio as a sensitive risk marker for atherosclerosis: Shimane CoHRE study. *Atherosclerosis.* 2015 Mar;239(1):61-6.
5. Dowsett L, Higgins E, Alanazi S, et al. ADMA: A Key Player in the Relationship between Vascular Dysfunction and Inflammation in Atherosclerosis. *J Clin Med.* 2020 Sep 20;9(9):3026.
6. Ye J, Dai Y, Mao H, Zheng W, et al. Prognostic value of asymmetric dimethylarginine in patients with coronary artery disease: A meta-analysis. Nitric Oxide. 2021 May 1;109-110:50-56.
7. Yu E, Ruiz-Canela M, Hu FB, et al. Plasma Arginine/Asymmetric Dimethylarginine Ratio and Incidence of Cardiovascular Events: A Case-Cohort Study. J Clin Endocrinol Metab. 2017 Jun 1;102(6):1879-1888.
8. Dong JY, Qin LQ, Zhang Z, et al. Effect of oral L-arginine supplementation on blood pressure: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Am Heart J.* 2011 Dec;162(6):959-65.
9. Bai Y, Sun L, Yang T, et al. Increase in fasting vascular endothelial function after short-term oral L-arginine is effective when baseline flow-mediated dilation is low: a meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2009 Jan;89(1):77-84.
10. Li H, Liu Q, Zou Z, et al. L-arginine supplementation to mitigate cardiovascular effects of walking outside in the context of traffic-related air pollution in participants with elevated blood pressure: A randomized, double-blind, placebo-controlled trial. *Environ Int.* 2021 Nov;156:106631.
11. Rezaei S, Gholamalizadeh M, Tabrizi R, et al. The effect of L-arginine supplementation on maximal oxygen uptake: A systematic review and meta-analysis. *Physiol Rep.* 2021 Feb;9(3):e14739.
12. Viribay A, Burgos J, Fernández-Landa J, et al. Effects of Arginine Supplementation on Athletic Performance Based on Energy Metabolism: A Systematic Review and Meta-Analysis. *Nutrients.* 2020 May 2;12(5):1300.
13. Fazelian S, Hoseini M, Namazi N, et al. Effects of L- Arginine Supplementation on Antioxidant Status and Body Composition in Obese Patients with Pre-diabetes: A Randomized Controlled Clinical Trial. *Adv Pharm Bull.* 2014 Oct;4(Suppl 1):449-54.
14. Daiber A, Kröller-Schön S, Oelze M, et al. Oxidative stress and inflammation contribute to traffic noise-induced vascular and cerebral dysfunction via uncoupling of nitric oxide synthases. *Redox Biol.* 2020 Jul;34:101506.
15. Mah E, Noh SK, Ballard KD, et al. Postprandial hyperglycemia impairs vascular endothelial function in healthy men by inducing lipid peroxidation and increasing asymmetric dimethylarginine:arginine. *J Nutr.* 2011 Nov;141(11):1961-8.
16. Monti LD, Galluccio E, Villa V, et al. Decreased diabetes risk over 9 year after 18-month oral L-arginine treatment in middle-aged subjects with impaired glucose tolerance and metabolic syndrome (extension evaluation of L-arginine study). *Eur J Nutr.* 2018 Dec;57(8):2805-2817.
17. Arlouskaya Y, Sawicka A, Głowala M, et al. Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA) Concentrations in Patients with Obesity and the Risk of Obstructive Sleep Apnea (OSA). *J Clin Med.* 2019 Jun 23;8(6):897.
18. Lenis YY, Elmetwally MA, Maldonado-Estrada JG, et al. Physiological importance of polyamines. *Zygote.* 2017 Jun;25(3):244-255.
19. Arribas-López E, Zand N, Ojo O, et al. The Effect of Amino Acids on Wound Healing: A Systematic Review and Meta-Analysis on Arginine and Glutamine. *Nutrients.* 2021 Jul 22;13(8):2498.
20. Schneider KL, Yahia N. Effectiveness of Arginine Supplementation on Wound Healing in Older Adults in Acute and Chronic Settings: A Systematic Review. *Adv Skin Wound Care.* 2019 Oct;32(10):457-462.
21. Martí I Líndez AA, Reith W. Arginine-dependent immune responses. *Cell Mol Life Sci.* 2021 Jul;78(13):5303-5324.
22. Moriguti JC, Ferriolli E, Donadi EA, et al. Effects of arginine supplementation on the humoral and innate immune response of older people. *Eur J Clin Nutr.* 2005 Dec;59(12):1362-6.
23. Atawia RT, Bunch KL, Toque HA, et al. Mechanisms of obesity-induced metabolic and vascular dysfunctions. *Front Biosci* (Landmark Ed). 2019 Mar 1;24:890-934.
24. Mousavi SM, Milajerdi A, Fatahi S, et al. The effect of L-arginine supplementation on obesity-related indices: A systematic review and meta-analysis of randomized clinical trials. *Int J Vitam Nutr Res.* 2021 Jan;91(1-2):164-174.
25. Hadi A, Arab A, Moradi S, et al. The effect of l-arginine supplementation on lipid profile: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr.* 2019 Nov 14;122(9):1021-1032.


**Supplement Facts**
**Serving Size: 1 Capsule**

| | Amount Per Serving | % Daily Value |
|---|---|---|
| L-Arginine HCl † | 700 mg | * |

*** Daily Value not established**

**Other ingredients:** Capsule shell (gelatin and water).

**CERTIFIED PURE**

**† Nonhydrolyzed, naturally produced, free-form L-Amino Acid**

**This product is gluten, dairy and GMO free.**

**RECOMMENDATION:** One (1) capsule three (3) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

**KEEP OUT OF REACH OF CHILDREN**
Store in a cool, dry area.
Sealed with an imprinted safety seal for your protection.


BIOTICS® RESEARCH CORPORATION

**(905)476-3554**

Biotics Research Canada
Box 283 Keswick On L4P 3E2
orders@bioticscan.com