## **Amino Acid Synergy**



Free-form Essential Amino Acids

By David M. Brady, ND, DACBN, IFMCP, FACN and Caitlin Higgins, MS, CNS

This information is provided as a medical and scientific educational resource for the use of physicians and other licensed health-care practitioners ("Practitioners"). This information is intended for Practitioners to use as a basis for determining whether to recommend these products to their patients. All recommendations regarding protocols, dosing, prescribing, and/or usage instructions should be tailored to the individual needs of the patient considering their medical history and concomitant therapies. This information is not intended for use by consumers.

Amino Acid Synergy provides targeted amounts of essential amino acids in their free form, meaning they are immediately available for absorption and can be put to metabolic use more readily and rapidly as compared to amino acids contained in dietary protein. Alpha-ketoglutarate and the bioactive form of vitamin B6 (as pyridoxal-5-phosphate [P5P]) are included to support amino acid metabolism and bioavailability. Tryptophan was not included in Amino Acid Synergy to give the health-care practitioner the ability to use this supplement regardless of the patient's serotonin-related status.

#### Highlights

- Balanced mix of readily absorbable, free-form, essential amino acids in targeted amounts
- Includes the bioactive form of vitamin B6 (as P5P) to support amino acid absorption, metabolism, and bioavailability
- Gluten-free, dairy-free, and soy-free
- Non-GMOs

Amino acids are fundamental for a vast array of metabolic processes, as they are the basic building blocks for more than 100,000 unique proteins in the human body. They serve as the nitrogenous backbones for compounds (e.g., neurotransmitters, hormones, enzymes) and as intermediates in cellular metabolism.<sup>1</sup> Amino acids also play a critical role in the metabolism and function of microorganisms in the gastrointestinal tract.<sup>2</sup> Insufficient amino acid absorption may be a result of dietary and lifestyle factors or digestive dysfunction, such as those that affect the proper functioning of the stomach, pancreas, liver, or small intestine.\* The precise amino acid content and sequence of a specific protein determines its biological activity. Proteins catalyze most reactions in living cells and control virtually all cellular processes.<sup>3</sup>

Humans can endogenously produce 11 (nonessential and conditionally essential amino acids) of the 20 amino acids de novo required for proper human physiology. The remaining nine essential amino acids (EAAs) are those whose carbon skeletons cannot be produced by human cells and must be supplied through food or supplementation to maintain nitrogen balance.<sup>3-5</sup> Unlike fatty acids and starches, the human body is unable to store excess amino acids for later use. Therefore, essential amino acids must be consumed in adequate amounts to help discourage the breakdown of body tissues that contain them, such as the skeletal muscle.\* Amino acid deficiency can have detrimental impacts on protein synthesis and whole-body homeostasis.<sup>6</sup>

Amino acids in their free form are immediately available for absorption, which can be put to metabolic use much more readily and rapidly than the amino acids in dietary protein. This may be especially beneficial for individuals with compromised digestive function (such as aging populations), those recovering from physical trauma and surgery individuals with difficulty consuming adequate amounts of complete protein

#### Benefits\*

- Supports protein status in the body
- Helps maintain lean body mass
- May promote muscle protein synthesis
- May help mitigate age-related muscle loss
- May be beneficial for individuals with difficulty consuming adequate amounts of complete protein and athletes who require additional amino acids

#### Supplement Facts Serving Size 4 capsules

Servings Per Container

Amount Per Serving		% Daily Value
Vitamin B-6 (as Pyridoxal-5-Phosphate)	14 mg	824%
L-Histidine	338 mg	1
L-Leucine	338 mg	*
Alpha-Ketoglutarate	300 mg	3
L-Arginine	300 mg	,
L-Lysine	300 mg	,
L-Phenylalanine	300 mg	,
L-Valine	300 mg	,
L-Isoleucine	270 mg	3
L-Methionine	270 mg	3
L-Threonine	270 mg	,

Other Ingredients: Cellulose (capsule), vegetable stearate.

surgery, individuals with difficulty consuming adequate amounts of complete protein, and athletes who require additional amino acids to maintain greater lean body mass.<sup>\*7-17</sup> Amino acids provided in their free form may also be useful for individuals in catabolic states due to stress or illness, along with elderly populations, especially those at risk of age-related muscle loss, and also for patients with confirmed amino acid deficiencies based on metabolic testing.<sup>\*18-28</sup>

According to a population-based, cross-sectional study from the 2014-2019 Korea National Health and Nutrition Examination Survey (KHANES) that included 5,971 participants  $\geq$ 65 years of age, higher total essential amino acid scores (based on 24-hour diet recall data) was associated with higher muscle strength.<sup>29</sup> Furthermore, increased total EAA intake from animal sources was shown to significantly enhance muscle strength compared to non-animal sources.<sup>29</sup> Another population-based, cross-sectional study of more than 25,000 participants  $\geq$ 30 years of age from 2008 to 2019 in the KHANES found that higher EAA intake was associated with significantly lower prevalence of metabolic syndrome, high blood pressure, and high triglyceride levels.<sup>30</sup>

Amino Acid Synergy provides eight of the nine EAAs in clinically useful amounts, including phenylalanine, valine, threonine, isoleucine, methionine, histidine, leucine, and lysine. It is also formulated with the conditionally essential amino acid, arginine, which plays an important role in trauma recovery, growth, development, regulation of gene expression,

immune function, and cell division.<sup>3,31</sup> Tryptophan was not included in Amino Acid Synergy to give the health-care practitioner the ability to use this supplement regardless of the patient's serotonin-related status and to allow the practitioner to add tryptophan (or 5-HTP Synergy<sup>™</sup> or 5-HTP Supreme<sup>™</sup>) on a case-by-case basis.

#### Ingredient Highlights

**L-Leucine** belongs to a special group of amino acids called branched-chain amino acids (BCAAs). BCAAs are required to help maintain and repair muscle tissue. Leucine is the most anabolic amino acid and leucine-enriched amino acid intake that has been shown to stimulate protein synthesis in skeletal muscle by activating the mammalian target of rapamycin (mTOR) signaling pathway.<sup>32,33</sup> Leucine is also necessary for the optimal growth of infants and for proper nitrogen balance in adults.

**L-Isoleucine** is another member of the BCAA family of amino acids. Isoleucine is needed for hemoglobin formation and helps to maintain regular energy metabolism. It is also important for helping to stabilize and regulate healthy blood sugar metabolism.<sup>1</sup>

**L-Valine** is another BCAA that is closely related to leucine and isoleucine in its structure and function. Valine is a constituent of fibrous protein in the body and functions to promote muscle growth and regeneration. One of its metabolites, β-aminoisobutyric acid, is secreted by skeletal muscle and acts on white adipose tissue to promote energy expenditure.<sup>33</sup>

In vitro and in vivo studies have shown that BCAA supplementation (either as a mixture or individually) may upregulate signaling pathways associated with mitochondrial biogenesis, such as PGC-1alpha. However, more well-controlled human clinical trials are needed to fully elucidate the function of BCAAs on mitochondrial biogenesis and cellular energetics.<sup>34</sup>

**L-Arginine** is considered a conditionally essential amino acid that plays an important role in cellular division, wound healing, and removing ammonia metabolites from the body. It is also important for healthy immune function, hormonal release, and nitric oxide production. In diet-induced obese rats, arginine supplementation was shown to enhance lipolysis and reduce oxidative stress in white adipose tissue and upregulated genes involved in mitochondrial biogenesis.<sup>31</sup>

**L-Histidine** is the direct precursor to histamine and is essential for normal growth and tissue repair, and it helps maintain the structure of the myelin sheaths that protect nerve cells. Histidine helps manufacture red and white blood cells and supports the body's ability to protect against the effects of heavy metals. Histamine is a biogenic amine and mediator of many biological processes, such as gastric secretions, vasodilation, inflammatory responses, bronchospasm, and neuromodulation.<sup>1</sup>

**L-Lysine** is required for proper growth and bone development in children and is essential to produce carnitine. Lysine also helps the body absorb and conserve calcium, and it plays an important role in the formation of collagen.<sup>1</sup>

**L-Methionine** is the first amino acid incorporated into the N-terminal position of all proteins, critically important for initiating messenger RNA translation. Methionine supplies sulfur and other compounds required by the body for normal metabolism, detoxification, and growth. Methionine reacts with adenosine triphosphate (ATP) to form S-adenosylmethionine (SAM), the principal methyl donor in the body and key cofactor to the synthesis of many important compounds, including epinephrine and choline.<sup>1</sup>

**L-Phenylalanine** is needed for the biosynthesis of proteins, catecholamine neurotransmitters, and melanin. It is a precursor to the amino acid L-tyrosine, which is then converted into the metabolite L-DOPA, dopamine, epinephrine, and norepinephrine.<sup>1</sup>

**L-Threonine** plays an important role in the regulation of protein balance, energy metabolism, and nutrient absorption. It is critical in the formation of protein, collagen, elastin, and tooth enamel, and it is also an important component of gastrointestinal mucin, which serves as a barrier in the gut. L-threonine is involved in the production of T-lymphocytes, a component of the immune system, and it facilitates lipotropic function and fat metabolism in the liver.<sup>1</sup>

**Vitamin B6** (as pyridoxal-5-phosphate [P5P]) is most well-known for its role in catalyzing many important steps in amino acid metabolism such as transamination, decarboxylation, and racemization.<sup>35</sup>

**Alpha-ketoglutarate** is the keto acid produced by deamination of glutamate and is a key intermediate in the citric acid cycle. It is one of the most important nitrogen transporters in the metabolic pathways. Furthermore, it is transaminated to form glutamine, which can then be decarboxylated into the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), a reaction that is facilitated by vitamin B6.

Recommended Use: Take 4 capsules per day between meals or as directed by your health-care practitioner.

Warning: Not recommended for individuals with phenylketonuria.

For a list of references cited in this document, please visit:

https://www.designsforhealth.com/api/library-assets/literature-reference---amino-acid-synergy-tech-sheet-references

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Healthcare practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

\*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.

To contact Designs for Health, please call us at (860) 623-6314 or visit us on the web at www.designsforhealth.com.

Designs for Health and logo are trademarks of Designs for Health, Inc. © 2023 Designs for Health, Inc. All rights reserved.

# **Amino Acid Synergy**



### References

- 1. Protein and Amino Acids. In: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2005:589-768.
- 2. Dai Z, Wu Z, Zhu W, Wu G. Amino acids in microbial metabolism and function. *Adv Exp Med Biol*. 2022;1354:127-143. doi:10.1007/978-3-030-85686-1\_7.
- Lopez MJ, Mohiuddin SS. Biochemistry, essential amino acids. [Updated 2022 Mar 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK557845/.
- 4. Hoffer LJ. Human protein and amino acid requirements. *JPEN J Parenter Enteral Nutr*. 2016;40(4):460-474. doi:10.1177/0148607115624084.
- 5. Phillips SM. Current concepts and unresolved questions in dietary protein requirements and supplements in adults. *Front Nutr.* 2017;4(13):1-10. doi:10.3389/fnut.2017.00013.
- 6. Wu G. Functional amino acids in nutrition and health. Amino Acids. 2013;45:407-411. doi:10.1007/s00726-013-1500-6.
- 7. Dunstan RH, Sparkes DL, Macdonald MM, et al. Diverse characteristics of the urinary excretion of amino acids in humans and the use of amino acid supplementation to reduce fatigue and sub-health in adults. *Nutr J.* 2017;16:19. doi:10.1186/ s12937-017-0240-y.
- 8. Furuta C, Murakami H. A novel concept of amino acid supplementation to improve the growth of young malnourished male rats. *Ann Nutr Metab.* 2018;72:231-240. doi:10.1159/000487603.
- 9. Volpato S, Custureri R, Puntoni M, et al. Effects of oral amino acid supplementation on multidimensional prognostic index in hospitalized older patients: a multicenter randomized, double-blind, placebo-controlled pilot study. *Clin Interv Aging*. 2018;13:633-640. doi:10.2147/CIA.S154998.
- 10. Elkind JA, Lim MM, Johnson BN, et al. Efficacy, dosage, and duration of action of branched chain amino acid therapy for traumatic brain injury. *Front Neurol.* 2015;6:73. doi:10.3389/fneur.2015.00073.
- 11. Katsanos CS, Madura JA II, Roust LR. Essential amino acid ingestion as an efficient nutritional strategy for the preservation of muscle mass following gastric bypass surgery. *Nutrition.* 2016;32(1):9-13. doi:10.1016/j.nut.2015.07.005.
- 12. Kido Y. The issue of nutrition in an aging society. *J Nutr Sci Vitaminol* (Tokyo). 2015(61):S176-S177. doi:10.3177/jnsv.61. S176.
- 13. Rémond D, Shahar DR, Gille D, et al. Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition. *Oncotarget.* 2015;6(16):13858-13898. doi:10.18632/oncotarget.4030.
- Mikkola TM, Salonen MK, Kajantie E, Kautiainen H, Eriksson JG. Associations of fat and lean body mass with circulating amino acids in older men and women. *J Gerontol A Biol Sci Med Sci.* 2019;75(5):885-891. doi.org/10.1093/ gerona/glz126.
- 15. Mitchell WK, Wilkinson DJ, Phillips BE, Lund JN, Smith K, Atherton PJ. (2016). Human skeletal muscle protein metabolism responses to amino acid nutrition. *Adv Nutr.* 2016;7(4):828S-838S. doi:10.3945/an.115.011650.
- 16. Jäger R, Kerksick CM, Campbell BI, et al. International society of sports nutrition position stand: protein and exercise. *J Int Soc Sports Nutr.* 2017;14(20):1-25. doi:10.1186/s12970-017-0177-8.
- 17. Wall BT, Cermak NM, van Loon LJ. Dietary protein considerations to support active aging. *Sports Med.* 2014;44:185-194. doi:10.1007/s40279-014-0258-7.
- 18. Weijs PJ, Cynober L, DeLegge M, Kreymann G, Wernerman J, Wolfe RR. Proteins and amino acids are fundamental to optimal nutrition support in critically ill patients. *Crit Care.* 2014;18(6):591. doi:10.1186/s13054-014-0591-0.
- 19. Fouque D, Chen J, Chen W, et al. Adherence to ketoacids/essential amino acids-supplemented low protein diets and new indications for patients with chronic kidney disease. *BMC Nephrol.* 2016;17(1):63. doi:10.1186/s12882-016-0278-7.
- 20. Ooi PH, Gilmour SM, Yap J, Mager DR. Effects of branched chain amino acid supplementation on patient care outcomes in adults and children with liver cirrhosis: a systematic review. *Clin Nutr ESPEN.* 2018;28:41-51. doi:10.1016/j.clnesp.2018.07.012.
- 21. Pasini E, Corsetti G, Aquilani R, et al. Protein-amino acid metabolism disarrangements: The hidden enemy of chronic age-related conditions. *Nutrients*. 2018;10(4):391. doi:10.3390/nu10040391.
- 22. Pasini E, Aquilani R, Dioguardi FS, D'Antona G, Gheorghiade M, Taegtmeyer H. Hypercatabolic syndrome: molecular basis and effects of nutritional supplementation with amino acids. *Am J Cardiol* 2008;101(11)(suppl 2):S11-S15. doi:10.1016/j.amjcard.2008.02.074.

- 23. Ruiz-Margáin A, Méndez-Guerrero O, Román-Calleja BM, González-Rodríguez S, Fernández-del-Rivero G, RodríguezCórdova PA, Macías-Rodríguez RU. Dietary management and supplementation with branched-chain amino acids in cirrhosis of the liver. *Rev Gastroenterol Mex.* 2018;83(4):424-433. doi.org/10.1016/j.rgmx.2018.05.006.
- 24. Kim HK, Suzuki T, Saito K, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. *J Am Geriatr Soc.* 2012;60(3):605. doi:10.1111/j.1532-5415.2011.03776.x.
- 25. Morley JE, Argiles JM, Evans WJ, et al. Society for sarcopenia, cachexia, and wasting disease. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc.* 2010;11(6):391-396. doi:10.1016/j. jamda.2010.04.014
- 26. Richter M, Baerlocher K, Bauer JM, et al, on behalf of the German Nutrition Society (DGE). Revised reference values for the intake of protein. *Ann Nutr Metab.* 2019;74(3):242-250. doi:10.1159/000499374.
- 27. Suga H, Hashimoto H. Age threshold for recommending higher protein intake to prevent age-related muscle weakness: a cross-sectional study in Japan. *PloS One*. 2018;13(12):1-11. doi:10.1371/journal.pone.0208169.
- 28. Beasley JM, Shikany JM, Thomson CA. The role of dietary protein intake in the prevention of sarcopenia of aging. *Nutr Clin Pract.* 2013;28(6):684-690. doi:10.1177/0884533613507607.
- 29. Im J, Park H, Park K. Dietary essential amino acid intake is associated with high muscle strength in Korean older adults. *Nutrients*. 2022;14(15):3104. doi:10.3390/nu14153104.
- 30. Im J, Park H, Park K. Higher intake of total dietary essential amino acids is associated with a lower prevalence of metabolic syndrome among Korean adults. *Nutrients*. 2022;14(22):4771. doi:10.3390/nu14224771.
- 31. Wu G. Functional amino acids in growth, reproduction, and health. Adv Nutr. 2010;1(1):31-37. doi:10.3945/an.110.1008.
- 32. Drummond MJ, Rasmussen BB. Leucine-enriched nutrients and the regulation of mammalian target of rapamycin signaling and human skeletal muscle protein synthesis. *Curr Opin Clin Nutr Metab Care*. 2008;11(3):222-226. doi:10.1097/MCO.0b013e3282fa17fb.
- 33. Sugimoto T, Kamei Y. Regulation of skeletal muscle function by amino acids, especially non-proteinogenic amino acids. *J Nutr Sci Vitaminol (Tokyo)*. 2022;68(suppl):S31-S33. doi:10.3177/jnsv.68.S31.
- 34. Hinkle JS, Rivera CN, Vaughan RA. Branched-chain amino acids and mitochondrial biogenesis: An overview and mechanistic summary. *Mol Nutr Food Res.* 2022;66(20):e2200109. doi:10.1002/mnfr.202200109.
- 35. Dalto DB, Matte JJ. Pyridoxine (vitamin B<sub>6</sub>) and the glutathione peroxidase system; a link between one-carbon metabolism and antioxidation. *Nutrients*. 2017;9(3):189. doi:10.3390/nu9030189.