



ArginMax – For Men

RESEARCH

Abstract

A Double-Blind Placebo-Controlled Study on the Effects of ArginMax, a Natural Nutritional Supplement for Enhancement of Male Sexual Function.

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Purpose: To evaluate the role of a natural nutritional supplement to enhance male sexual function as a follow-up to a previously published pilot study examining the effects of ArginMax on sexual health.

Materials and Methods: Seventy-three (73) subjects participated in the study with twenty-five (25) subjects participating in the pilot arm, and forty-eight (48) subjects participating in the double-blind placebo-controlled arm of the study. This abstract will review the double-blind placebo-controlled study.

Forty-three (48) study participants, ages 31-73, enrolled through a urology clinic were evaluated over a 4-week period. Subjects were enrolled consecutively with participation open to all individuals diagnosed with mild, moderate, to severe erectile dysfunction of varying etiology. The study instrument was the International Index of Erectile Function (I.I.E.F.), a validated instrument with multidimensional scale for assessment of erectile function used in the evaluation of Viagra (sildenafil citrate). Upon enrollment, subjects were randomly assigned active or placebo in a double-blind fashion resulting in twenty-four (24) subjects placed on active and twenty-four (24) subjects placed on placebo. The age of the ArginMax group ranged from 41 to 73, the age of the placebo group ranged from 31 to 73. The average age of the ArginMax group was 60.5, the average age of the placebo group was 61.0. There were 4 diabetic participants in the ArginMax group, and 3 diabetic participants in the placebo group. There were 7 participants with hypertension in the ArginMax group, and 8 participants with hypertension in the placebo group.

ArginMax is a proprietary nutritional supplement which incorporates a standardized combination of ginkgo biloba (24% flavone glycosides, 6% terpene lactones), Korean ginseng (Panax Ginseng-30% ginsenosides), American ginseng (Panax Quinquefolius- 5% ginsenosides), L-arginine (precursor to nitric oxide), along with vitamins B6, B12, folate, thiamin, riboflavin, niacin, biotin, pantothenic acid, antioxidant vitamins A, C, E, selenium, and Zinc.

Results: 87.5% of subjects in the ArginMax group reported improvement in ability to maintain an erection during intercourse, while 22.2% reported improvement in the placebo group. 75.0% of subjects in the ArginMax group reported improvement in satisfaction with their overall sex life, while 20.8% reported improvement in the placebo group. No headaches, nausea, vomiting, stomach upset, visual disturbance, blood pressure alterations, dizziness, or other significant side effects were noted in either group.

Discussion: The results of this double-blind placebo-controlled study are consistent with the findings of the ArginMax pilot study where twenty-five (25) men with mild to moderate erectile dysfunction were placed on a four week course of ArginMax. In the pilot study, 88.9% of the participants improved in ability to maintain an erection during intercourse, and 75% improved in their satisfaction with overall sex life.

Nitric oxide (NO) is central to smooth muscle relaxation, vascular dilatation, and the regulation of circulation and erection. L-arginine, a naturally occurring amino acid, is the precursor of nitric oxide. Supplementation with L-arginine provides the substrate for nitric oxide production by endothelial cells. The conversion of L-arginine to nitric oxide is mediated by an enzyme, nitric oxide synthase (NOS). Certain botanical extracts with a long history of use in traditional medicine have been observed to facilitate the conversion of L-arginine into nitric oxide. One observed mechanism for increase in nitric oxide production in endothelial cells is stimulation of the NOS enzyme activity by ginsenosides—a primary active class of ingredient extracted from ginseng. Ginkgo biloba has a well established role in facilitating micro-vascular circulation with evidence suggesting that it may directly promote smooth muscle relaxation in the corpus cavernosum via its action on the nitric oxide pathway.

Hence, the presence of a highly specific combination of these natural botanical extracts and L-arginine, the precursor of N.O., promotes the production of nitric oxide which serves to optimize circulation and erection. The proposed mechanism of action of ArginMax is through up-regulation of the L-arginine/nitric oxide pathway.

Conclusion: The role of nutritional supplements for sexual health is an infrequently discussed yet extremely important subject matter. Nutritional supplementation can play a major role in sexual health. It is critical to recognize that as consumers develop an ever increasing interest in a wellness oriented approach towards healthcare, the role of nutritional supplementation for one of the most important biological functions of life—sexual health—be addressed. After all, if we take a calcium supplement for our bones, and a vitamin E supplement for our heart, why not a nutritional supplement for our sexual health?

This arena will be further evaluated via the continuation of the current study as part of a large-scale multi-center study of ArginMax.

Review of the Medical Literature

The following is a review of selective scientific literature pertaining to ArginMax ingredients.

It is well established that nitric oxide (NO) is the key mediator for the up-regulation of cGMP which in turn mediates erectile function.¹ L-arginine is the precursor of nitric oxide. The conversion of L-arginine to nitric oxide is mediated by nitric oxide synthase (NOS). Increasing tissue L-arginine levels results in the increase of NO and cGMP.^{2,3} Supplementation with L-arginine has been shown to play a role in restoring endothelial-derived nitric oxide production in many disorders in which endothelial-derived nitric oxide is reduced or impaired, including impairment resulting from diabetes and hypercholesterolemia.^{4,5,6,7,8} Studies also point to the role of L-arginine as not only a substrate for NOS in the up-regulation of cGMP, but also acts to reduce cell-mediated breakdown of nitric oxide.⁹

The efficacy of Korean ginseng (Panax Ginseng) in treating erectile dysfunction was recently demonstrated in a randomized controlled clinical trial involving a total of 90 patients studied over 3 months, 30 each receiving placebo, trazadone, or ginseng.¹⁰ Ginseng was the most efficacious treatment with improvements measured in erectile parameters such as girth, libido, and patient satisfaction. Frequency of intercourse, ejaculations, and erections did not differ among groups. In a controlled study with 66 patients, Panax ginseng was demonstrated to increase spermatozoa count and motility in 66 patients with fertility problems.¹¹ Ginsenosides (the primary active component of ginseng) have been shown to increase NO production in endothelial cells.^{12,13,14} One observed mechanism for increase in NO production is up-regulation of NOS activity by ginsenosides.¹⁴ The effects of ginsenosides on NO production has implications for improved sexual function, and may partly account for the aphrodisiac effect of Panax ginseng used in traditional Chinese medicine.

Ginkgo biloba is well established to facilitate microvascular circulation¹⁵ which may physiologically lead to improvement of erections. In addition to ginkgo biloba's ability to facilitate microvascular circulation, potentially benefiting erectile function through enhanced vascular blood flow, there is evidence that ginkgo biloba extract may also directly elucidate smooth muscle relaxation in the corpus cavernosum, likely via effects on the nitric oxide pathway.^{16,17}

B-complex vitamins are important to the activity of hundreds of enzymes and in energy metabolism. Low levels of circulating folate and vitamin B6 confer an increased risk of peripheral vascular disease,¹⁸ leading to potential reduction of erectile function.

Zinc is a fundamental mineral in the maintenance of human reproductive function. Low levels of serum zinc has been shown to cause sexual dysfunction and associated with infertility in males.^{19,20} Zinc deficiency during growth periods result in lack of gonadal development in males.^{21,22} Zinc deficiency leads to depletion of testosterone and inhibition of spermatogenesis.²³ Zinc is also thought to help extend the functional life span of ejaculated spermatozoa.²³

Selenium has a key influence on spermatozoa numbers and motility. It is an essential element in normal spermatozoa development. Selenium is incorporated in the sperm mitochondria capsule and may thus affect the behavior and function of the spermatozoon.²⁴ It has been shown that dietary supplementation with selenium-vitamin E statistically significantly increases sperm motility, percent live, and percent normal spermatozoa.²⁵

It is well established that one of the key roles of seminal plasma is the protection of spermatozoa against reactive oxygen species.²⁶ In a study of 101 patients seeking consultation for infertility and 15 fertile donors, a strong inverse relationship was found between total reactive antioxidant potential in seminal plasma and infertility.²⁶

A pilot clinical study was undertaken to preliminarily evaluate the role of a combinatorial nutritional product which incorporates the previously discussed key ingredients for optimization of nitric oxide production and enhancement of sexual function. In the pilot study,^{32,33,34,35} twenty-five study participants were consecutively enrolled through a urology clinic with participation open to all individuals diagnosed with mild to moderate erectile dysfunction of varying etiology. The study instrument was the International Index of Erectile Function (IIEF). Following the completion of the study, 88.9% of the subjects experienced improvement in ability to maintain an erection during intercourse, and 75.0% experienced improvement in satisfaction with their overall sex life.^{32,33,34,35}

The results of the pilot clinical study indicate that an expansion of the study to a larger population with a double-blind placebo-controlled protocol is the logical next step in exploring the sexual function benefits of ArginMax, and the basis for the present study.^{36,37}

Bibliography

1. Burnett AL. Nitric oxide control of lower genitourinary tract functions: a review. *Urology* 1995 Jun;45(6):1071-1083.
2. Jung HC, Mun KH, Park TC, Lee YC, Park JM, Huh K, Seong DH, Suh JK. Role of nitric oxide in penile erection. *Yonsei Med J* 1997 Oct;38(5):261-269.
3. Kimura K, Takahashi M, Naroda T, Iriguchi H, Miyamoto T, Kawanishi Y, Numata A, Yuasa M, Tamura M, Kagawa S. The relaxation of human corpus cavernosum caused by nitric oxide. *Nippon Hinyokika Gakkai Zasshi* 1993 Sep;84(9):1660-1664.
4. Creager MA, Gallagher SJ, Girend XJ, Coleman SM, Dzau VJ, Cooke JP. L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. *J Clin Invest* 1992 Oct;90(4):1248-1253.
5. Pieper GM, Dondlinger LA. Plasma and vascular tissue arginine are decreased in diabetes: acute arginine supplementation restores endothelium-dependent relaxation by augmenting cGMP production. *J Pharmacol Exp Ther* 1997 Nov;283(2):684-691.
6. Wascher TC, Graier WF, Dittrich P, Hussain MA, Bahadori B, Wallner S, Toplak H. Effects of low-dose L-arginine on insulin-mediated vasodilatation and insulin sensitivity. *Eur J Clin Invest* 1997 Aug;27(8):690-695.
7. Pieper GM, Siebeneich W, Dondlinger LA. Short-term oral administration of L-arginine reverses defective endothelium-dependent relaxation and cGMP generation in diabetes. *Eur J Pharmacol* 1996 Dec 19;317(2-3):317-320.
8. Moody JA, Vernet D, Laidlaw S, Rajfer J, Gonzalez-Cadavid NF. Effects of long-term oral administration of L-arginine on the rat erectile response. *J Urol* 1997 Sep;158(3 Pt 1):942-947.
9. Wascher TC, Posch K, Wallner S, Hermetter A, Kostner GM, Graier WF. Vascular effects of L-arginine: anything beyond a substrate for the NO-synthase? *Biochem Biophys Res Commun* 1997 May 8;234(1):35-38.
10. Choi HK, Seong DH, Rha KH. Clinical efficacy of Korean red ginseng for erectile dysfunction. *Int J Impot Res* 1995 Sep;7(3):181-186.
11. Salvati G, Genovesi G, Marcellini L, Paolini P, De Nuccio I, Pepe M, Re M. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. *Panminerva Med* 1996 Dec;38(4):249-254.

12. Chen X. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. *Clin Exp Pharmacol Physiol* 1996 Aug;23(8):728-732.
13. Han SW, Kim H. Ginsenosides stimulate endogenous production of nitric oxide in rat kidney. *Int J Biochem Cell Biol* 1996 May;28(5):573-580.
14. Chen X, Lee TJ. Ginsenosides-induced nitric oxide-mediated relaxation of the rabbit corpus cavernosum. *Br J Pharmacol* 1995 May;115(1):15-18
15. Auguet M, Delaflotte S, Hellegouarch A, Clostre F. Pharmacological bases of the vascular impact of Ginkgo biloba extract. *Presse Med* 1986 Sep 25;15(31):1524-1528.
16. Paick JS, Lee JH. An experimental study of the effect of ginkgo biloba extract on the human and rabbit corpus cavernosum tissue. *J Urol* 1996 Nov;156(5):1876-1880.
17. Chen X, Salwinski S, Lee TJ. Extracts of Ginkgo biloba and ginsenosides exert cerebral vasorelaxation via a nitric oxide pathway. *Clin Exp Pharmacol Physiol* 1997 Dec;24(12):958-959.
18. Robinson K, Arheart K, Refsum H, Brattstrom L, Boers G, Ueland P, Rubba P, Palma-Reis R, Meleady R, Daly L, Witteman J, Graham I. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. *Circulation* 1998 Feb 10;97(5):437-443
19. Khedun SM, Naicker T, Maharaj B. Zinc, hydrochlorothiazide and sexual dysfunction. *Cent Afr J Med* 1995 Oct;41(10):312-315.
20. Mohan H, Verma J, Singh I, Mohan P, Marwah S, Singh P. Inter-relationship of zinc levels in serum and semen in oligospermic infertile patients and fertile males. *Indian J Pathol Microbiol* 1997 Oct;40(4):451-455.
21. Prasad AS. Zinc: an overview. *Nutrition* 1995 Jan;11(1 Suppl):93-99.
22. Nishi Y. Zinc and growth. *J Am Coll Nutr* 1996 Aug;15(4):340-344.
23. Bedwal RS, Bahuguna A. Zinc, copper and selenium in reproduction. *Experientia* 1994 Jul 15;50(7):626-640.
24. Hansen JC, Deguchi Y. Selenium and fertility in animals and man--a review. *Acta Vet Scand* 1996;37(1):19-30.
25. Vezina D, Mauffette F, Roberts KD, Bleau G. Selenium-vitamin E supplementation in infertile men. Effects on semen parameters and micronutrient levels and distribution. *Biol Trace Elem Res* 1996;53(1-3):65-83.
26. Smith R, Vantman D, Ponce J, Escobar J, Lissi E. Total antioxidant capacity of human seminal plasma. *Hum Reprod* 1996 Aug;11(8):1655-1660.
27. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997 Jun;49(6):822-830.
28. The Derogatis Interview for Sexual Functioning (DISF/DISF-SR): an introductory report. *Derogatis LR. J Sex Marital Ther* 1997;23(4):291-304.
29. Conte HR. Development and use of self-report techniques for assessing sexual functioning: a review and critique. *Arch Sex Behav* 1983 Dec;12(6):555-576.
30. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993 May 29;306(6890):1437-1440.
31. Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS *BMJ* 1993 May 29;306(6890):1440-1444.
32. Ito T, Kawahara K, Das A. The Effects of Arginmax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. On-line proceedings of the 5th Internet World Congress on Biomedical Science at McMaster University, hosted by INABIS, the Internet Association for Biomedical Sciences, December, 1998.
33. Ito T, Kawahara K, Das A. The Effects of Arginmax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. *Hawaii Medical Journal*. December, 1998, Vol. 57, No. 12, p.741-744..
34. Ito T, Kawahara K, Das A. The Effects of Arginmax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. Presentation at the 4th Asian Congress of Urology, September, 1998.
35. Ito T, Kawahara K, Das A. The Effects of Arginmax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. Presentation at the American Urological Association (AUA) New York Section Meeting, October, 1998.
36. Ito T, Kawahara K, Das A. A Double-Blind Placebo-Controlled Clinical Study on the Effects of ArginMax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. Presentation at the 14th International Congress of Sexology, August, 1999.
37. Ito T, Kawahara K, Das A. A Double-Blind Placebo-Controlled Clinical Study on the Effects of ArginMax, a Natural Dietary Supplement for Enhancement of Male Sexual Function. Presentation at the 1999 American Urological Association (AUA) Western Section Meeting, September, 1999.