Oral L-Citrulline Supplementation Improves Erection Hardness in Men With Mild Erectile Dysfunction

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OBJECTIVES To test the efficacy and safety of oral L-citrulline supplementation in improving erection hardness in patients with mild erectile dysfunction (ED). L-arginine supplementation improves nitric oxide-mediated vasodilation and endothelial function; however, oral administration has been hampered by extensive presystemic metabolism. In contrast, L-citrulline escapes presystemic metabolism and is converted to L-arginine, thus setting the rationale for oral L-citrulline supplementation as a donor for the L-arginine/nitric oxide pathway of penile erection.

METHODS In the present single-blind study, men with mild ED (erection hardness score of 3) received a placebo for 1 month and L-citrulline, 1.5 g/d, for another month. The erection hardness score, number of intercourses per month, treatment satisfaction, and adverse events were recorded.

RESULTS A total of 24 patients, mean age 56.5 ± 9.8 years, were entered and concluded the study without adverse events. The improvement in the erection hardness score from 3 (mild ED) to 4 (normal erectile function) occurred in 2 (8.3%) of the 24 men when taking placebo and 12 (50%) of the 24 men when taking L-citrulline ($P < .01$). The mean number of intercourses per month increased from 1.37 ± 0.93 at baseline to 1.53 ± 1.00 at the end of the placebo phase ($P = .57$) and 2.3 ± 1.37 at the end of the treatment phase ($P < .01$). All patients reporting an erection hardness score improvement from 3 to 4 reported being very satisfied.

CONCLUSIONS Although less effective than phosphodiesterase type-5 enzyme inhibitors, at least in the short term, L-citrulline supplementation has been proved to be safe and psychologically well accepted by patients. Its role as an alternative treatment for mild to moderate ED, particularly in patients with a psychologically fear of phosphodiesterase type-5 enzyme inhibitors, deserves further research. UROLOGY 77: 119–122, 2011. © 2011 Elsevier Inc.

Nitric oxide (NO) is a physiologic signal essential to penile erection, because it acts both as a neurotransmitter in the penile nonadrenergic noncholinergic nerve fibers and as a vasodilator of smooth muscle cells of the penile arteries, sinusoids, and trabeculae.[1,2] NO activates soluble guanylate cyclase to convert guanosine triphosphate to cyclic guanosine monophosphate (cGMP), which in turn causes penile smooth muscle relaxation. The erection occurs when the sinusoids engorged with blood compress the subtunical veins to closure, thus trapping blood within the penis. The erection eventually subsides when cGMP has been hydrolyzed to inactive GMP by phosphodiesterase type 5 enzymes (PDE-5).

PDE-5 inhibitors, which increase penile smooth muscle relaxation by preventing cGMP hydrolysis, represent a safe and effective oral treatment of erectile dysfunction (ED); however, their cost, contraindications, and fear, more than the occurrence, of side effects have limited their use. Nutrients acting as NO donors would therefore represent an attractive alternative to the use of PDE-5 inhibitors.

The NO donor L-arginine is a semiessential amino acid present in dietary proteins and produced in the body from L-citrulline, another semiessential amino acid synthesized in the intestinal tract from glutamine.[3] NO synthase isoforms convert L-arginine to NO, which activates the cGMP pathway, and L-citrulline, which can be reconverted by the kidneys into L-arginine to restart a NO-producing cycle.[4] Thus, L-arginine causes in vitro[5] relaxation of isolated corpus cavernosum tissue. In a double-blind placebo-controlled study testing L-arginine versus placebo in men with ED, however, subjective improvement was reported by 31% of men taking L-

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arginine and 12% of men taking placebo.[6] Although no patients in that study reported side effects, oral administration of L-arginine in high doses could result in nausea, vomiting, diarrhea, headache, flushing and numbness,[7] owing to intestinal and hepatic conversion of L-arginine to ornithine and urea.

L-citrulline, conversely, escapes intestinal or liver metabolism, enters the kidneys and is rapidly converted into L-arginine. It has recently been shown that oral L-citrulline supplementation increases the plasma L-arginine concentration and augments NO-dependent signaling in a dose-dependent manner,[8] thus providing the rationale for oral L-citrulline supplementation as a donor for the L-arginine/NO pathway in patients with ED.

The present placebo-controlled pilot trial aimed to determine whether oral L-citrulline supplementation improved erection hardness in patients with mild ED.

MATERIAL AND METHODS

Men >18 years old who had presented from January to May 2009 at our andrology outpatient clinic with a history of ED of ≥3 months' duration were considered eligible for the present single-blind, placebo-controlled, prospective pilot study. We sought to concentrate on patients reporting a mild to moderate reduction of penile rigidity that still allowed some kind of vaginal penetration but not satisfactory penetration and/or completion of successful intercourse. This situation has been well depicted by an erection hardness score (EHS) of 3.

The EHS is a simple, validated,[9] single-item, patient-reported outcome that measures erection hardness (Table 1), an essential component of erectile function (EF) and correlates well with the International Index of Erectile Function-Erectile Function domain (the standard instrument to categorize ED severity), the Sexual Experience Questionnaire (designed to capture EF and individual and couple satisfaction), and the Self-Esteem and Relationship questionnaire (designed to assess self-esteem and the overall relationship).[10,11] An EHS of 4 corresponds to the best outcome on the International Index of Erectile Function, Sexual Experience Questionnaire, and Self-Esteem and Relationship questionnaire. Improvement in the EHS from 3, suggestive of mild ED, to 4, suggestive of normal EF,[9] has been associated with a 24-greater odds of successful intercourse.[11]

Therefore, the inclusion criteria for the present study were an EHS of 3 at both the screening and the enrollment visit, a stable heterosexual relationship, and an interest in improving sexual function by entering the study protocol and adhering to the scheduled follow-up visits. The exclusion criteria were severe cardiovascular disease, recent cerebrovascular accidents, renal or hepatic insufficiency, psychiatric or severe neurologic disorders, untreated endocrine disease, previous radical prostatectomy, significant penile deformity, and previous or current treatment of ED. The study was performed in accordance with the standards of Helsinki Declaration, the local ethical committee approved the study, and all patients provided written informed consent.

Table 1. Erection hardness score

How Would You Rate the Hardness of Your Erection?	Score
Penis does not enlarge	0
Penis is larger but not hard	1
Penis is hard but not enough for intercourse	2
Penis is hard enough for penetration but not completely hard	3
Penis is completely hard and fully rigid	4

The screening visit included a detailed medical and sexual history, EHS, and a complete physical examination. The enrollment visit included a second EHS and evaluation of routine blood tests. The enrolled patients received a placebo for the first month and L-citrulline, 1.5 g/d in 2 doses, for the second month. The drug and placebo were both prepared by the hospital pharmaceutical department and looked exactly the same. The patients were asked to keep a sexual activity diary that listed every attempt of intercourse and the date, sexual satisfaction, and possible adverse events (AEs). Follow-up visits were scheduled at the end of months 1 (the end of the placebo phase) and 2 (the end of the treatment phase) to evaluate changes in the physical examination findings, EHS, number of intercourses per month, treatment satisfaction (very satisfied, satisfied, not satisfied), and possible AEs. At the month 2 visit, the patients were informed they had received a commercially available nutrient and given the possibility to continue it, if interested, or to receive a prescription for a PDE-5 inhibitor.

Statistical Analysis

The data are presented as the mean ± standard deviation and were analyzed using the Student t test to compare the mean values and the chi-square test to compare 2 proportions, using StatSoft, version 8.0 (StatSoft, Tulsa, OK). Significance was set at $P < .05$.

RESULTS

Of the 24 eligible patients (mean age 56.5 ± 9.8 years), all agreed to enter the study, and all concluded it without AEs. The most common concomitant medical conditions were consistent with those generally associated with ED, including hypertension (37.5%), hypercholesterolemia (21%), benign prostatic hyperplasia (12.5%), and diabetes mellitus (12.5%).

Significant improvement in the EHS from 3 to 4 was reported by 2 (8.3%) of the 24 men when taking the placebo and 12 (50%) of the 24 men when taking L-citrulline ($P < .01$). The mean number of intercourses per month, a nonvalidated patient-reported outcome we have commonly used in patients treated for ED, was 1.37 ± 0.93 at baseline, 1.53 ± 1.00 at the end of the placebo phase ($P = .57$), and 2.3 ± 1.37 at the end of the treatment phase ($P < .01$). For treatment satisfaction, all 12 patients reporting an EHS improvement from 3 to 4 scored very satisfied, and the remaining 12 scored not satisfied and all asked for a PDE-5 inhibitor prescription at the end of the study phase. Finally, no AEs occurred.

COMMENT

The results from the present placebo-controlled pilot trial showed that 1 month of treatment with oral L-citrulline was

able to improve erection hardness enough to restoring normal EF (EHS 4) in 12 of 24 patients with mild ED (EHS 3) of varying origins. In particular, the EHS increased from 3 to 4 in 8.3% of men taking placebo and 50% of men taking L-citrulline; this difference reached statistical significance ($P < .01$), despite the small sample size.

Grounds exist to assume that such beneficial effects of L-citrulline supplementation on erectile function resulted from an increase in corpus cavernosum L-arginine availability, leading to increased activity of the L-arginine/NO/cGMP-mediated mechanisms of vasodilation and penile smooth muscle relaxation. It has recently been shown that increased NO production induces corpus cavernosum smooth muscle cell synthesis and secretion of vascular endothelial growth factor (VEGF), which can restore impaired endothelial function. Also, L-arginine, the precursor of NO, has been shown to provide the substrate for the NO/cGMP/VEGF pathway,[12] thus providing the rationale for L-arginine supplementation, not only to treat ED, but also to attempt to reverse penile endothelial dysfunction.

Attempts at treating ED with oral L-arginine supplementation, however, have been limited by the unsatisfactory results obtained and the availability of effective oral therapy represented by PDE-5 inhibitors. We found only one randomized controlled trial testing L-arginine supplementation for ED that was published in 1999,[6] at the beginning of the PDE-5 inhibitor era. In that study, in which 50 patients with organic ED were randomized to receive placebo or 5 g L-arginine daily for 6 weeks, significant subjective improvement was reported by 31% of the men taking L-arginine and 12% of the men taking the placebo. Subjective improvement was not associated with hemodynamic changes in corpus cavernosum circulation, as assessed by penile duplex ultrasonography. The lack of hemodynamic changes was attributed to insufficient intracavernosal concentration of L-arginine and/or the lack of delivery of L-arginine to the corpus cavernosum when administered orally.[6] Oral L-arginine supplementation has been known to be hampered by extensive presystemic elimination by intestinal bacteria and intestinal and hepatic arginase activity that converts L-arginine to ornithine and urea.[13] In contrast, oral L-citrulline escapes intestinal and liver metabolism, inhibits arginase activity,[13] and is converted by the kidneys into L-arginine, thus providing plenty of substrate for the L-arginine/NO/cGMP/VEGF pathway.[8]

Although the present study is, to the best of our knowledge, the first to test the efficacy and safety of oral L-citrulline supplementation in the management of ED, evidence has already shown that oral L-citrulline supplementation might reverse the endothelial dysfunction associated with sickle cell disease[14] and pulmonary hypertension,[15] thus confirming that such a nutrient can effectively activate the L-arginine/NO/cGMP/VEGF pathway.

Another interesting finding of our study was that all patients reporting improvement in their EHS elected to continue with L-citrulline treatment, but the others, reporting no improvement and thus scoring not satisfied, asked for a PDE-5 inhibitor prescription. This was probably because L-citrulline supplementation had no side effects and was psychologically well accepted, because it was perceived by patients as a nutrient and not a drug. Moreover, this finding has further confirmed the importance of the EHS as a measure of both treatment efficacy and patient satisfaction.

Although prospective and placebo controlled, the present study had some limitations. First, no attempt was made to distinguish whether the ED was either organic or psychogenic; however, this was reflective of what commonly occurs in real-life clinical practice. Second, we did not plan to compare the subjective with objective findings, such as changes in penile endothelial or hemodynamic function, because of the complex and invasive nature of these measurements. Third, we did not test longer treatment periods nor compare the efficacy of L-citrulline with that of PDE-5 inhibitors, because we believed these objectives were beyond the scope of a pilot study.

CONCLUSIONS

Oral L-citrulline supplementation for 1 month was able to improve erection hardness enough to restore normal EF in 12 of 24 patients with mild ED. Although less effective than PDE-5 inhibitors, at least in the short term, L-citrulline supplementation proved to be safe and was psychologically well accepted by patients. Its role as an alternative and less expensive (<€15/mo) treatment for mild to moderate ED, particularly for patients psychologically fearing PDE-5 inhibitors, deserves additional research.

References

1. Burnett AL, Lowenstein CJ, Bredt DS, et al. Nitric oxide: a physiologic mediator of penile erection. *Science*. 1992;257:401-403.
2. Burnett AL. Novel nitric oxide signalling mechanisms regulate the erectile response. *Int J Impot Res Suppl*. 2004;1:S15-S19.
3. Ligthart-Melis GC, van de Poll MC, Boelens PG, et al. Glutamine is an important precursor for de novo synthesis of arginine in humans. *Am J Clin Nutr*. 2008;87:1282-1289.
4. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. *Biochem J*. 1998;336:1-17.
5. Gur S, Kadowitz PJ, Trost L, et al. Optimizing nitric oxide production by time dependent L-arginine administration in isolated human corpus cavernosum. *J Urol*. 2007;178:1543-1548.
6. Chen J, Wollman Y, Chernichovsky T, et al. Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study. *BJU Int*. 1999;83:269-273.
7. Grimble GK. Adverse gastrointestinal effects of arginine and related amino acids. *J Nutr*. 2007;17(suppl 2):1693-1701.
8. Schwedhelm E, Maas R, Freese R, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol*. 2008;65:51-59.
9. Mulhall JP, Goldstein I, Bushmakin AG, et al. Validation of the erection hardness score. *J Sex Med*. 2007;4:1626-1634.

10. King R, Juenemann KP, Levinson IP, et al. Correlation between increased erection hardness and improvement in emotional well-being and satisfaction outcomes in men treated with sildenafil citrate for erectile dysfunction. *Int J Impot Res*. 2007;19:398-406.
11. Cappelleri JC, Bushmakin AG, Symonds T, et al. Scoring correspondence in outcomes related to erectile dysfunction treatment on a 4-point scale (score 4). *J Sex Med*. 2009;6:809-819.
12. Komori K, Tsujimura A, Takao T, et al. Nitric oxide synthesis leads to vascular endothelial growth factor synthesis via the NO/cyclic guanosine 3′,5′-monophosphate (cGMP) pathway in human corpus cavernosal smooth muscle cells. *J Sex Med*. 2008;5:1623-1635.
13. Morris SM Jr. Enzymes of arginine metabolism. *J Nutr*. 2004;134: 2743S-2747S.
14. Waugh WH, Daeschner CW, Files BA, et al. Oral citrulline as arginine precursor may be beneficial in sickle cell disease: early phase two results. *J Natl Med Assoc*. 2001;93:363-371.
15. Smith HA, Canter JA, Christian KG, et al. Nitric oxide precursors and congenital heart surgery: a randomized controlled trial of oral citrulline. *J Thorac Cardiovasc Surg*. 2006;132:58-65.