

# High-dose arginine may increase liver inflammation in ASA deficiency

**In addition to its role in the urea cycle, argininosuccinate lyase (ASL) is also essential for endogenous (produced within the body) synthesis of arginine. Patients affected by ASA deficiency can have liver involvement ranging from liver enlargement (hepatomegaly) with elevations of liver enzymes to severe liver fibrosis. The standard of care for patients with ASA deficiency has historically included arginine supplementation that compensates for the decreased endogenous synthesis in addition to promoting the excretion of nitrogen (ammonia) as argininosuccinic acid. Results of a recent study suggest a lower dose of arginine combined with sodium phenylbutyrate may help reduce liver dysfunction in ASA deficiency.**

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...high dose arginine may lead to higher liver inflammation in patients with ASA.

Researchers hypothesized that if increased levels of argininosuccinic acid were the predominant cause for liver dysfunction, a high dose of therapeutic arginine (500mg/kg/day) would be associated with worsening of liver functions as compared to a low dose of arginine (100mg/kg/day) combined with sodium phenylbutyrate, which would result in lower levels of argininosuccinic acid levels. To evaluate the effects of these two treatments on liver function in patients with ASA, a randomized double-blind placebo controlled cross-over trial was carried out by Dr. Brendan Lee and his team at Baylor as part of the Urea Cycle Disease Consortium research. Eleven patients completed both arms of the trial and were included in the analysis.

As expected, patients had significantly increased levels of phenylacetylglutamine and phenylacetic acid while on low-dose arginine with sodium phenylbutyrate, and higher plasma arginine and citrulline levels while on high-dose arginine. Ammonia control was comparable between the two arms of the trial. Patients had statistically significant increases in plasma ASA levels while on high-dose arginine. AST levels were also increased in the high-dose arginine arm. Patients with abnormal liver transaminases seemed to have the most increase in liver enzymes while on high-dose arginine. The function of the liver as assessed by PT, INR, Factors VII, IX and fibrinogen were comparable between the two arms of the study.

These results reveal that high dose arginine may lead to higher liver inflammation in patients with ASA, especially in patients with existing liver dysfunction. The results have therapeutic implications, as they suggest it may be optimal to treat ASA patients who have liver dysfunction with lower doses of arginine combined with sodium phenylbutyrate. ■

## References

Nagamani SC, Shchelochkov OA, Mullins MA, Carter S, Lanpher BC, Sun Q, Kleppe S, Erez A, O'Brian Smith E, Marini JC, Lee B, Members of the Urea Cycle Disorders Consortium. A randomized controlled trial to evaluate the effects of high-dose versus low-dose arginine therapy on hepatic function tests in argininosuccinic aciduria. *Mol Genet Metab* 2012 Nov; 107(3):315-21. Epub 2012 Sep 17. PMID 23040521