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Arginine Therapy Shows Promise for Treatment of Sickle Cell Disease Clinical Subphenotypes of Hemolysis and Arginine Deficiency

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I read with interest “Arginase Inhibition Reverses Endothelial Dysfunction, Pulmonary Hypertension, and Vascular Stiffness in Transgenic Sickle Cell Mice”¹. Alterations in the arginine metabolome have been extensively studied in sickle cell disease (SCD), in humans as well as in SCD-transgenic mice². Although Stepan and colleagues suggest that supplementing L-arginine does not improve nitric oxide (NO) bioavailability¹, a more comprehensive review of the literature suggests benefits resulting from L-arginine therapy that are likely NO-related². Pulmonary hypertension (PH), leg ulcers and vaso-occlusive pain are SCD-clinical subphenotypes of arginine deficiency that are reversed with arginine supplementation². Anecdotal cases of immediate improvement in SCD-associated priapism in the emergency department setting have also been reported². Low arginine bioavailability is also associated with poor survival³. In SCD-transgenic mouse models, arginine supplementation inhibits red cell Gardos channels, reduces red cell density, improves perfusion, and reduces inflammation, lung injury, microvascular vaso-occlusion and mortality. Arginine supplementation also increases erythrocyte glutathione levels in both mouse and human trials⁴.

When arginine is given to SCD patients at steady-state, a paradoxical decrease in NO metabolites (NO_x) occurs that is not overcome by higher doses, indicating that arginine is metabolized differently in SCD compared to control subjects. However, when arginine is given during acute pain, a complication associated with an abrupt drop in arginine bioavailability, a robust dose-dependent increase in NO_x is observed. This suggests that arginine is also metabolized differently in SCD at steady-state compared to times of acute illness². Similar observations were made with respect to arginine pharmacokinetics in moderate compared to severe malaria, suggesting that a greater consumption of arginine occurs when the disease state is more severe.

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Claudia R. Morris, MD, is the inventor or co-inventor of several UCSF-Benioff Children's Hospital Oakland patents/patent-pending applications that include nutritional supplements, and biomarkers of cardiovascular disease related to arginine bioavailability, is an inventor of an Emory University School of Medicine patent application for a nutritional supplement, is a consultant for Pfizer, NourishLife, LLC, Nestle Nutritional Institute and Calithera Biosciences, Inc, and has received research support from MAST Therapeutics, the United States Food and Drug Administration, and the National Institutes of Health.

This Letter references off-label use of L-arginine and of arginase inhibitors.

Little and colleagues⁴ provided arginine supplementation to SCD patients with a mean tricuspid regurgitate jet velocity (TRV) of 2.57m/s on Doppler echocardiography, which is precariously close to the normal value of TRV<2.5m/s. Based on studies comparing right heart cardiac catheterization to echocardiography, few if any of those patients likely had true PH. However, when arginine therapy is given to patients with clinical symptoms of PH and a mean TRV=3.47m/s, a >15% reduction in estimated pulmonary artery pressures occurred after only 5 days of oral therapy (Figure 1)⁵. Our previous work has demonstrated that a significant decrease in arginine bioavailability occurs in SCD patients with a TRV 2.9m/s, a scenario when PH is more likely and mortality risk is significantly increased².

For arginine-deficiency syndromes like SCD, improved arginine bioavailability through arginine supplementation may restore important physiologic processes; however, metabolism by excess arginase may limit its potential to maximally impact NO synthesis. Stepan and colleagues report promising results, as arginase inhibition improved NO bioavailability and attenuated systemic and pulmonary vascular endothelial dysfunction in SCD-transgenic mice¹. Therefore, arginase represents a potential therapeutic target in the treatment of SCD-related cardiovascular dysfunction in addition to arginine therapy. Future studies evaluating a combination of arginine together with an arginase inhibitor are also worth investigation.

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Figure 1.

Changes in the estimated mean pulmonary artery systolic pressures (mm Hg) measured by Doppler echocardiography in patients with sickle cell disease and pulmonary hypertension risk. Measurements are taken before arginine therapy is started (pretreatment) and after completion of 15 doses of arginine (post-treatment). Male patients are represented by *circles*, and females are represented by *triangles*. The *dotted line* represents the only patient found to be noncompliant based on posttreatment plasma arginine levels. Arginine supplementation significantly decreases pulmonary artery systolic pressures ($n=10$, $p<0.005$). Reprinted with

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