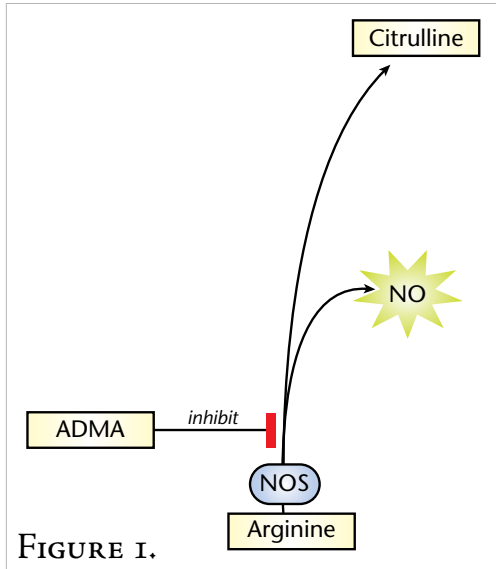


ADMA

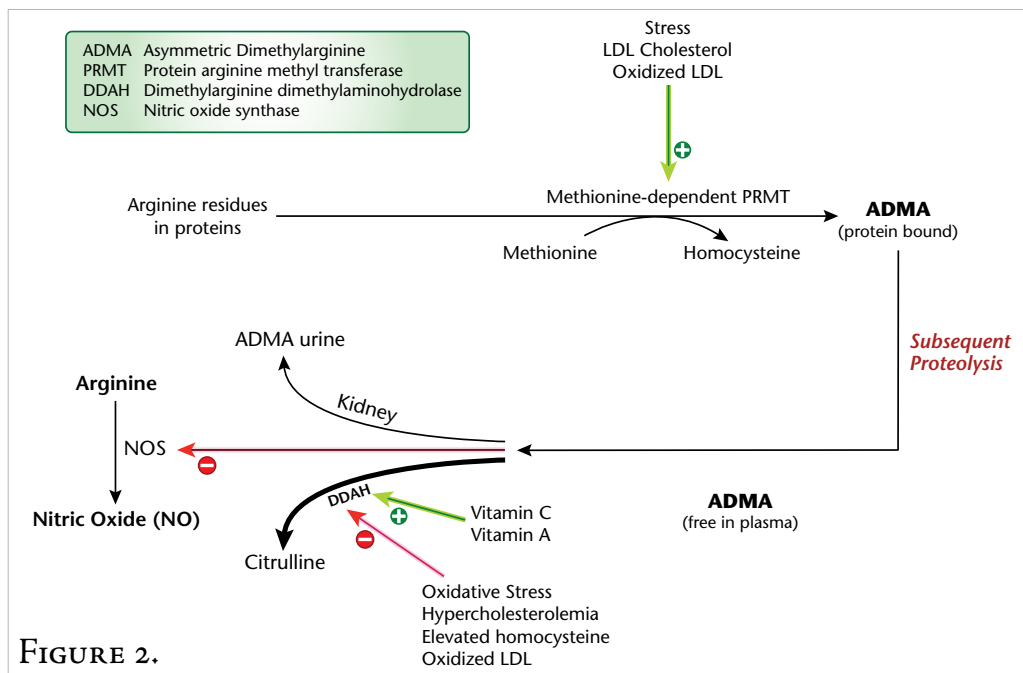
ADMA (asymmetric dimethylarginine) is an endogenous nitric oxide synthase (NOS) inhibitor. NOS produces nitric oxide (NO) and citrulline, from arginine (Figure 1). High levels of ADMA result in lower levels of NO and elevated arginine. NO is a vasodilator and lower levels can lead to increases in blood pressure. By inhibiting NO production, ADMA may impair blood flow, accelerate atherogenesis, and interfere with angiogenesis.



ADMA is produced by all cells. It is formed by the methylation of protein bound arginine residues by the enzyme methionine-dependent protein arginine N-methyltransferase (PRMT) (Figure 2).

Methylation reactions require the conversion of methionine to homocysteine. Several animal and clinical studies have demonstrated a strong association between homocysteine, ADMA, and endothelial dysfunction.¹ Methionone supplementation can lead to increases in ADMA, an effect that can be reversed by supplementing with vitamin C. ADMA can be reduced by decreasing PRMT activity.² PRMT is primarily expressed in cardiovascular endothelial and smooth muscle cells. Stress, LDL cholesterol and oxidized LDL have been shown to increase PRMT activity resulting in increased ADMA. ADMA inhibits NO formation by NOS. The majority of ADMA is metabolized to citrulline by dimethylarginine dimethylaminohydrolase (DDAH) and about 10% of ADMA is excreted by the kidneys.² Degradation to citrulline is inhibited by hypercholesterolemia, oxidized LDL, elevated homocysteine, and hyperglycemia.

Reducing ADMA or reversing its effects is becoming a goal for pharmacotherapeutic interventions. Administration of arginine has been shown to improve endothelium-dependent vascular functions in subjects with high ADMA levels.³ Estrogens have also been found to reduce plasma levels of ADMA.



Increased plasma ADMA is an independent cardiovascular risk factor. Elevated levels of ADMA have also been found in renal failure,^{4,5} hypertension, hypercholesterolemia, preeclampsia,⁶ diabetes mellitus,⁷ tobacco use, PCOS,⁸ and aging.⁹ High cholesterol diets have also been associated with elevated plasma ADMA.

Metamatrix recently participated in research that evaluated data from the PREVENCIÓN Study. It was done by J.A. Chirinos et. al. at the University of Pennsylvania, and is published in *Hypertension*, 2008, volume 52.¹⁰ In the study, 922 adults were examined; ADMA and L-arginine were found to be associated with various classic cardiovascular risk factors. LDL, CRP, and age were each independent positive predictors of ADMA levels. CRP and HDL were positive predictors of arginine, age and male gender were negative predictors. ADMA (but not L-arginine) was a significant predictor of carotid intima-media thickness ($r=0.31$; $p=0.002$), even after adjustment for cardiovascular risk factors, CRP, and renal function. Higher arginine independently predicted systolic hypertension.

Targeted biochemical interventions in ADMA metabolism have been shown to have a positive short-term effect in cardiovascular heart disease (CHD) risk factors. Dietary components certainly influence vascular functions, and a high-fat meal has been shown to increase postprandial plasma ADMA levels. High amounts of dietary carbohydrates have been found to be strongly associated with low levels of plasma ADMA. Specific nutrient recommendations are listed in the table below.

IF ADMA IS HIGH:

- Add arginine – Check levels with the plasma amino acid test which also shows citrulline level. Three to six grams of arginine daily increases NO production.
- Add vitamin A and C – Decreases oxidative stress to increase conversion to citrulline. Vitamin E has also been found to be beneficial. Antioxidants speed breakdown of ADMA.
- Add folate, B12, and B6 -- Increases methylation and lowers homocysteine.
- Evaluate cardiac markers and markers of inflammation – Lowers LDL, oxidized LDL, and cholesterol.
- Avoid or decrease alcohol.
- Decreasing high fat meals and increasing health carbohydrates may be also be beneficial.

REFERENCES

1. Dayal S, Lentz SR. ADMA and hyperhomocysteinemia. *Vasc Med*. 2005 Jul;10 Suppl 1:S27-33
2. David E.L. Wilcken, Ah Siew Sim, Jun Wang, Xing Li Wang. Asymmetric dimethylarginine (ADMA) in vascular, renal and hepatic disease and the regulatory role of l-arginine on its metabolism. *Molecular Genetics and Metabolism* Volume 91, Issue 4, August 2007, Pages 309-317.
3. Böger RH. Asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, explains the “L-arginine paradox” and acts as a novel cardiovascular risk factor. *J Nutr*. 2004 Oct;134(10 Suppl):2842S-2847S
4. Al Banchaabouchi M, Marescau B, Possemiers I, D’Hooge R, Levillain O, De Deyn PP. NG, NG-dimethylarginine and NG, NG-dimethylarginine in renal insufficiency. *Pflugers Arch*. 2000;439(5):524-531.
5. Kielstein JT, Böger RH, Bode-Böger SM, et al. Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol*. 1999;10(3):594-600.
6. Böger RH, Bode-Böger SM, Szuba A, et al. Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. *Circulation*. 1998;98(18):1842-1847.
7. Fard A, Tuck CH, Donis JA, et al. Acute elevations of plasma asymmetric dimethylarginine and impaired endothelial function in response to a high-fat meal in patients with type 2 diabetes [In Process Citation]. *Arterioscler Thromb Vasc Biol*. 2000;20(9):2039-2044.
8. Taner Ozgurtas, Cagatay Oktenli, Murat Dede. Metformin and oral contraceptive treatments reduced circulating asymmetric dimethylarginine (ADMA) levels in patients with polycystic ovary syndrome (PCOS). Volume 200, Issue 2, October 2008, Pages 336-344.
9. Böger RH, Bode-Böger SM, Thiele W, Junker W, Alexander K, Frolich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease [see comments]. *Circulation*. 1997;95(8):2068-2074.
10. Julio A. Chirinos, Robert David, J. Alexander Bralley. Endogenous Nitric Oxide Synthase Inhibitors Arterial Hemodynamics, and Subclinical Vascular Disease The PREVENCIÓN Study. *Hypertension*. 2008;52:1-9.