

ADMA, cardiovascular disease, and diabetes

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Background

Asymmetric dimethylarginine (ADMA) is a naturally occurring endogenous L-arginine metabolite with the capacity to inhibit all three isoforms of nitric oxide (NO) synthases. ADMA and, to a greater extent, its stereoisomer symmetrical dimethylarginine (SDMA), which has no effect on NO synthases, have been reported to accumulate in patients with renal failure.¹ Chronic elevation of ADMA in animals causes atherosclerotic lesions and renal damage as a consequence of reduced NO generation. This suggests an important role for ADMA in explaining the relationship between endothelial dysfunction, atherosclerosis, and diabetic nephropathy. It has been shown that ADMA is increased in conditions such as impaired renal function, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), hypertension, morbid obesity, arterial occlusive disease, and diabetic nephropathy. More recently, ADMA levels have been shown to be predictive of severe cardiovascular events and all-cause mortality in predominantly nondiabetic chronic kidney disease, end-stage renal disease (ESRD), and cardiovascular disease (CVD).

Unfortunately, a specific pharmacological treatment to reduce ADMA is not available. However, lifestyle interventions such as endurance training or weight loss in morbidly obese patients² initiated for reducing cardiovascular risk can significantly decrease circulating ADMA concentrations. Clinical and experimental studies suggest that treatment with metformin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can lower circulating ADMA concentrations.^{3,4}

ADMA and diabetes

Elevated ADMA concentrations have been described in patients with T1DM⁵ and T2DM,⁶ and in particular in those patients presenting with diabetic nephropathy or micro- and macroalbuminuria.^{5,6} In a prospective follow-up study, 397 T1DM patients⁷ with overt diabetic nephropathy were followed for a median of 11.3 years. Elevated ADMA levels predicted an increased rate of decline in the glomerular filtration rate, development of ESRD, and all-cause mortality ($P < 0.001$). In a prospective follow-up study including 125 patients with T2DM,⁸ patients with baseline ADMA or C-reactive protein (CRP)

in the highest tertile had a significantly increased hazard ratio (HR) for incident CVD events compared with those with ADMA or CRP in the lowest tertile (HR, 3.63 [$P = 0.002$] and HR, 2.37 [$P = 0.038$], respectively). The HR was particularly high when both ADMA and CRP were in the highest tertile compared with patients with neither ADMA nor CRP in the highest tertile (HR, 4.59; $P < 0.001$). Elevated ADMA levels have also been found in T2DM patients with diabetic retinopathy.⁹ This is of interest in relation to recent findings suggesting a link between diabetic retinopathy and stroke,¹⁰ heart failure,¹¹ coronary calcium,¹² and CVD.¹³

In conclusion, ADMA is an emerging independent risk marker for future CVD events. The clinical acceptance of this parameter will depend on the availability of a therapy to directly decrease ADMA, which could then confirm the role of ADMA as a causal risk factor. Further studies are warranted in

patients with diabetes, especially regarding the possible effects of ADMA on diabetes-associated complications.

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References:

- 1.** Zoccali C. *J Hypertens.* 2006;24:611-619.
- 2.** Krzyzanowska K, Mittermayer F, Kopp H-P, et al. *J Clin Endocrinol Metab.* 2004;89:6277-6281.
- 3.** Heutling D, Schulz H, Nickel I, et al. *J Clin Endocrinol Metab.* 2008;93:82-90.
- 4.** Scalera F, Martens-Lobenhoffer J, Bukowska A, et al. *Hypertension.* 2008;51:696-703.
- 5.** Tarnow L, Hovind P, Teerlink T, et al. *Diabetes Care.* 2004;27:765-769.
- 6.** Krzyzanowska K, Mittermayer F, Shnawa N, et al. *Diabet Med.* 2007;24:81-86.
- 7.** Lajer M, Tarnow L, Jorsal A, et al. *Diabetes Care.* 2008;31:747-752.
- 8.** Krzyzanowska K, Mittermayer F, Wolzt M, et al. *Diabetes Care.* 2007;30:1834-1839.
- 9.** Malecki MT, Undas A, Cyganek K, et al. *Diabetes Care.* 2007;30:2899-2901.
- 10.** Baker ML, Hand PJ, Wang JJ, et al. *Stroke.* 2008;39:1371-1379.
- 11.** Cheung N, Wang JJ, Rogers SL, et al. *J Am Coll Cardiol.* 2008;51:1573-1578.
- 12.** Reaven PD, Emanuele N, Moritz T, et al. *Diabetes Care.* 2008;31:952-957.
- 13.** Targher G, Bertolini L, Zenari L, et al. *Diabet Med.* 2008;25:45-50.