

Asymmetric dimethylarginine: a risk indicator or pathogenic factor?

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Asymmetric dimethylarginine (ADMA), a dimethylated derivative of arginine, acts as an endogenous inhibitor of nitric oxide (NO $\cdot$) synthase because of its structural similarity to the primary substrate of the enzyme, namely, arginine. Thus, accumulation of ADMA may counteract the vasodilatory effect exerted by NO $\cdot$. As a consequence, blood pressure may increase in patients with elevated circulating ADMA levels, which leads to development of endothelial dysfunction. Indeed, increased ADMA levels have been related to increased cardiovascular and overall mortality in patients undergoing coronary angiography in several studies.^{1,2}

In patients infected with human immunodeficiency virus type 1 (HIV-1) infection, elevated concentrations of dimethylarginines, (ie, ADMA) and also of symmetric dimethylarginine (SDMA) have been documented. In the current issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)*, Szymanek-Pasternak et al³ present data on serum ADMA levels in HIV-1-infected patients with or without significant renal disease.

Their findings of increased ADMA levels in patients with HIV-1 infection are concordant with earlier data that showed a strong relationship between ADMA levels and the macrophage activation marker neopterin.⁴ In this study, combined antiretroviral therapy (ART) led to a significant drop of ADMA levels. By contrast, Szymanek-Pasternak et al³ did not find any significant difference between treated and untreated patients, which differs from the earlier report. In addition, they reported that risk factors for chronic kidney disease do not influence the serum levels of ADMA.³

In the previous study,⁴ the statistical analysis was performed by paired tests since all specimens were collected at baseline before the introduction of ART and after 6 months of therapy. Thus, potential interindividual differences did not play any role, but those could be important in the new study,³ which was performed in

a cross-sectional design, and also variable treatment duration could have an impact.

Oxidative stress, endothelial NO $\cdot$ synthase inhibition, uncoupling, inflammation, and shear stress play a pivotal role in ADMA-pathobiochemistry by affecting protein arginine methyltransferases/dimethylarginine dimethylaminohydrolase expression and NO $\cdot$ synthesis and leading to a common result—endothelial dysfunction. Endothelial dysfunction seems to be the common finding in studies investigating the role of ADMA in cardiovascular disease. ADMA is significantly associated with risk factors for cardiovascular disease and shows strong, independent prognostic value for mortality and future cardiovascular events.

In the earlier study, successful ART, reflected by decreasing HIV RNA levels, led to decreasing levels of methylated arginines and immune activation markers, while lipid concentrations normalized. It was concluded that disturbances of dimethylarginine metabolism are unlikely to account for the increased risk of cardiovascular events of HIV-infected patients under ART and that the increase of ADMA is more a bystander than a player.⁴ A similar conclusion can be drawn from the recent findings by Szymanek-Pasternak,³ ADMA does not seem to play a role in the development of renal dysfunction in patients with HIV-1 infection receiving ART. In this regard, also SDMA measurements could provide some interesting information, since it has been proposed as a better endogenous marker of renal function than ADMA.⁵

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Received: August 12, 2016.
Accepted: August 12, 2016.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2016; 126 (9): 621-622
doi:10.20452/pamw.3572
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