Lowering Asymmetric Dimethylarginine – A New Mechanism Mediating the Renoprotective Effects of Renin-Angiotensin System Inhibitors in Proteinuric Patients?

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The use of ACE inhibitors and angiotensin receptor blockers (ARBs) has been proven to offer renal and cardiovascular protection beyond their blood pressure lowering capacity [1, 2]. Therefore, current guidelines recommend them as first-line treatment for hypertension and proteinuria in chronic kidney disease (CKD) [3]. The favorable renal effects of blocking the renin-angiotensin system are thought to be mediated by modifying renal and intraglomerular hemodynamics, by reducing proteinuria and ameliorating oxidative stress. Importantly, the degree of proteinuria decrease is associated with the degree of renal and cardiovascular protection: the more proteinuria reduction, the more protection [4]. In this issue of Blood Purification, Yilmaz et al. [5] report an interesting hypothesis-generating study in which a new potential pathway for renoprotection of the renin-angiotensin system blockade in proteinuric CKD patients is proposed. The authors investigate the effect of an ACE inhibitor and an ARB in 66 proteinuric, nondiabetic patients with stage 3 CKD. Aside from proteinuria, the endogenous nitric oxide inhibitor asymmetric dimethylarginine (ADMA) as well as its structural isomer symmetric dimethylarginine (SDMA), HOMA and insulin levels and CRP were measured. Endothelial function was assessed by flow-mediated vasodilation. Both substances, the ACE inhibitor and the ARB lead to similar improvements of the biochemical markers as well as to enhancement of flow-mediated vasodilation. Interestingly, at baseline, the degree of proteinuria was independently related to ADMA and SDMA levels. Moreover, logistic regression analysis suggested that the 35% drop in ADMA levels in this study was related to the improvement of proteinuria.

Despite all the limitations of this nonrandomized uncontrolled study, the authors point out a new and potentially important pathway by which proteinuria and renal injury could be linked. A reduction of proteinuria by blocking the renin-angiotensin system could cause a decrease in ADMA (and SDMA), potentially increasing the bioavailability of nitric oxide. This effect seems to be independent of the changes in blood pressure.

What is ADMA?

ADMA is a naturally occurring amino acid that inhibits the activity of nitric oxide synthase (NOS). ADMA is produced by methylation of arginine residues in intracellular proteins via protein arginine N-methyltransferases. When these proteins are hydrolyzed, ADMA is released. ADMA is excreted in the urine but the primary route of ADMA clearance is the enzymatic degradation by dimethylamine dimethylaminohydrolase (DDAH). DDAH
converts ADMA to citrulline and dimethylamine. Several studies showed that ADMA is an excellent predictor of mortality in patients with and without renal disease [6, 7]. Additionally, ADMA is considered to mediate the deleterious effects of classical and modern cardiovascular risk factors [8]. SDMA, the structural isomer of ADMA, stems also from degradation of methylated proteins but seems to be solely eliminated by renal excretion. It is currently considered to be endogenous marker of excretory renal function [9]. In contrast to ADMA, it has no direct effect on NOS activity but indirectly hinders NOS activity by interfering with the transport of the NOS substrate, i.e. L-arginine, into the cells [10].

Why Is It Important to Lower ADMA Levels in Patients with CKD?

Several studies coherently showed that ADMA is elevated in patients with CKD [11], even before impairment of excretory renal function is present [12]. Two studies indicated that ADMA is involved in the progression of CKD [13, 14]. In both studies, high ADMA levels predicted a faster rate of renal function loss. Several preclinical and clinical data point to possible mechanisms of how ADMA may cause renal injury. Infusion of exogenous ADMA increases systemic vascular resistance [15, 16], elevates mean arterial pressure [15, 16], decreases heart rate [15, 16] and reduces cardiac output [15, 16] in men. In addition, ADMA administration dose-dependently impairs renal blood flow and sodium reabsorption [16]. Exogenous ADMA also decreases cerebral perfusion and increases vascular stiffness [17]. In contrast, lowering ADMA by increasing the activity of DDAH, the main enzyme degrading ADMA, ameliorates morphological and functional renal injury in rats [18].

Is There a Special Effect of Renin-Angiotensin System Inhibition on ADMA in Proteinuria?

Several small studies had previously indicated that ADMA can be lowered by both, ACE inhibitors and ARBs in essential hypertension [19]. However, a study in a larger number of type 2 diabetics without proteinuria could not confirm this finding [20]. Yilmaz et al. [5] show a more pronounced decrease in plasma ADMA than in other previous studies. ACE inhibitors reduce progression to renal failure better when proteinuria is higher [21]. This holds even true for nondiabetic patients with CKD that are at low risk for cardiovascular disease [22]. In contrast, the absence of proteinuria seems to inhibit the beneficial effect of ACE inhibitors [22]. The fact that proteinuria reduction is associated with a decrease in ADMA levels might help to explain this phenomenon.

Is DDAH the Key Regulator of ADMA Levels in Proteinuria?

Yilmaz et al. [5] describe that a decrease in proteinuria is accompanied by a decrease in both, ADMA and SDMA. This is important as DDAH, which only lowers ADMA but not SDMA, is thought to be the key regulator of plasma ADMA levels. If both methylarginines, ADMA and SMDA change this concomitantly, a different mechanism seems to be involved. An altered protein turnover/protein arginine N-methyltransferase activity (systemically or locally) could change the production/liberation of ADMA and SDMA as it had been shown for endothelial cells in vitro [23].

The multifaceted aspects of cardiovascular disease in renal impairment with proteinuria are unlikely to be explained by one gene, mechanism or mediator. However, the endogenous NOS inhibitor ADMA seems not only to be an ideal laboratory and clinical marker of cardiovascular disease but might also represent an important pathway mediating the adverse vascular effects of proteinuria.

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References


