Role of asymmetric dimethylarginine in cardiovascular disease and diabetes

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'...ADMA is an emerging independent risk marker for future cardiovascular events.'

The endogenous competitive nitric oxide (NO) synthase inhibitor asymmetric dimethylarginine (ADMA) is a naturally occurring amino acid [1]. It is produced by methylation of protein-bound L-arginine, which is catalyzed by protein arginine methyltransferases [2]. It is partly eliminated from the organism by renal filtration. In healthy individuals, approximately 10% of this methylated arginine is excreted via this mechanism. The predominant mode of elimination of ADMA occurs via enzymatic degradation by dimethylarginine dimethylaminohydrolase (DDAH) to citrulline and dimethylamine [3].

ADMA & cardiovascular disease

Asymmetric dimethylarginine causes endothelial dysfunction in forearm resistance arteries [4]. It increases the systemic vascular resistance and arterial blood pressure and decreases cardiac output [5]. Owing to its biological actions and the considerable high concentrations found in patients with renal insufficiency, the relationship between ADMA and cardiovascular complications was first studied in these high-risk patients. In a prospective study, Zoccali *et al.* found a significant association between circulating ADMA and future cardiovascular events and mortality [6]. Other studies observed elevated ADMA in patients with normal or slightly impaired renal function and an adverse cardiovascular risk profile, including patients with peripheral arterial occlusive disease [7], hypertension [8], hyperlipidemia [9], insulin resistance [10], Type 2 diabetes mellitus [11], Type 1 diabetes mellitus [12], patients with diabetic nephropathy [13,14], patients with hypopituitarism [15] or women with previous gestational diabetes [16]. Several studies have reported a predictive value of ADMA for cardiovascular events. The occurrence of cardiovascular end points in high-risk patients has been found to be directly and independently associated with elevated ADMA concentrations in

patients with coronary artery disease [17], peripheral arterial occlusive disease [18], Type 2 diabetes mellitus [19], Type 1 diabetes [20] and chronic heart failure [21]. A particularly strong relationship between ADMA and hemodynamic parameters, as well as clinical outcome has been observed in patients with pulmonary arterial hypertension [22].

Interestingly, results from animal experiments suggest that ADMA is not only a risk marker but also a risk factor for cardiovascular events. It was demonstrated that continuous infusion of ADMA led to the development of microvascular lesions in coronary vessels of mice [23]. Overexpression of the ADMA-degrading enzyme, DDAH, reduced ADMA in mice and reduced graft coronary artery disease [24]. Furthermore, DDAH overexpression prevented progression of renal dysfunction by inhibiting loss of peritubular capillaries and tubulointerstitial fibrosis in rats with chronic kidney disease [25]. Konishi *et al.* showed that transgenic mice with DDAH overexpression exhibited enhanced endothelial cell regeneration and neointima formation after vascular injury [26]. These findings imply that ADMA may directly contribute to vascular organ damage.

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Nevertheless, it remains to be determined whether a direct alteration of ADMA concentrations can reduce cardiovascular risk in humans. A specific pharmacological treatment to reduce ADMA is not yet available. However, it was demonstrated that other measures to reduce cardiovascular risk, including endurance training in patients with Type 1 diabetes [27] and in patients with elevated cardiovascular risk [28], or weight loss in morbidly obese patients [29], can decrease circulating ADMA concentrations. *In vitro* experiments indicate that some drugs (e.g., pravastatin, telmisartan or pioglitazone) can increase the activity or the production of the enzyme DDAH and thereby reduce ADMA [30–32]. Clinical studies also report that treatment with metformin, ACE inhibitors, angiotensin receptor

blockers or α -lipoic acid can lower circulating ADMA concentrations [33–39]. The literature on the effect of statins and glitazones on ADMA is controversial [40–46]. While one trial reported an ADMA reduction during treatment with rosiglitazone, this was not observed in a different cohort [10,47]. However, it remains speculative whether modulation of ADMA by these treatments will also directly impact cardiovascular risk.

‘There are also data that demonstrated that insulin resistance is related to elevated concentrations of ADMA.’

ADMA & diabetes

Patients with diabetes have an adverse cardiovascular risk profile. Elevated ADMA concentrations have been described in patients with Type 2 and Type 1 diabetes [11,12]. Hyperglycemia *per se* may increase ADMA concentrations. One *in vitro* study demonstrated that elevated glucose levels are capable of inhibiting DDAH activity in cultured endothelial cells [40]. Clinical investigations in patients also indicate that ADMA is directly related to blood glucose levels [11,48]. As demonstrated in a recent study, strict glycemic control may exert anti-atherogenic effects by reducing ADMA levels in patients with Type 2 diabetes [49]. There are also data that demonstrated that insulin resistance is related to elevated concentrations of ADMA [10]. Recent evidence suggests that elevated ADMA concentrations are associated with glycemic control in different patient populations, which fits with the assumption that ADMA may serve as risk predictor for cardiovascular events [50,51].

Besides associations between ADMA and metabolic control, ADMA might also play an important role for the development of diabetic complications. ADMA is elevated in patients with Type 1 and Type 2 diabetes and diabetic nephropathy with micro- and macroalbuminuria [12,14]. ADMA is related to the progression of renal disease and might therefore have potentially adverse effects in patients with diabetic nephropathy [52,53]. Furthermore, elevated ADMA levels have been described in Type 2 diabetic patients with retinopathy [54]. Therefore, it is tempting to speculate that ADMA might act as a pathophysiologically relevant factor for diabetes-associated complications. Nevertheless, hyperglycemia remains a major cause for both increased ADMA and the development of diabetic complications, which makes the interpretation of the data more complex.

In conclusion, ADMA is an emerging independent risk marker for future cardiovascular events. The clinical acceptance of this parameter will depend on the availability of a therapy to directly decrease ADMA, which could 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.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties

No writing assistance was utilized in the production of this manuscript.

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