The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor

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Abstract

There is abundant evidence that the endothelium plays a crucial role in the maintenance of vascular tone and structure. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthase. ADMA inhibits vascular NO production at concentrations found in pathophysiological conditions (i.e., 3–15 μmol/l); ADMA also causes local vasoconstriction when it is infused intraarterially. The biochemical and physiological pathways related to ADMA are now well understood: dimethylarginines are the result of the degradation of methylated proteins; the methyl group is derived from S-adenosylmethionine. Both ADMA and its regioisomer, SDMA, are eliminated from the body by renal excretion, whereas only ADMA, but not SDMA, is metabolized via hydrolytic degradation to citrulline and dimethylamine by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). DDAH activity and/or expression may therefore contribute to the pathogenesis of endothelial dysfunction in various diseases. ADMA is increased in the plasma of humans with hypercholesterolemia, atherosclerosis, hypertension, chronic renal failure, and chronic heart failure. Increased ADMA levels are associated with reduced NO synthesis as assessed by impaired endothelium-dependent vasodilation. In several prospective and cross-sectional studies, ADMA evolved as a marker of cardiovascular risk. With our increasing knowledge of the role of ADMA in the pathogenesis of cardiovascular disease, ADMA is becoming a goal for pharmacotherapeutic intervention. Among other treatments, the administration of L-arginine has been shown to improve endothelium-dependent vascular function in subjects with high ADMA levels.

Keywords: Endothelium; Nitric oxide; Coronary heart disease; Prognosis; Oxidative stress

1. Introduction

Traditional risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes account for up to 80% of excess risk for coronary events [1,2]. However, in certain groups of patients with a high cardiovascular event rate, a larger proportion of premature coronary artery disease may remain unexplained by these factors [3]. Novel risk factors have been identified in recent years [4], and our growing understanding of the process of atherogenesis is increasingly leading to the identification of the underlying molecular mechanisms. One central arena in which the early functional changes begin, eventually leading to atherosclerotic plaque formation, is the endothelial cell [5].

There is abundant evidence that the endothelium plays a crucial role in the maintenance of vascular tone and structure. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO). NO is formed in the endothelium by the endothelial isoform of nitric oxide synthase (NOS) [6]. NO is involved in a broad variety of regulatory mechanisms of the cardiovascular system. Besides inducing vasodilatation, it inhibits the adhesion
Fig. 1. Nitric oxide (NO) exerts pleiotropic effects on the cardiovascular system. It has been shown to induce endothelium-dependent vasodilation, to inhibit platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation. NO also exerts anti-oxidant effects, resulting in reduced vascular superoxide radical generation and diminished oxidation of LDL cholesterol. As all of these mechanisms are known to contribute to the pathogenesis of atherosclerosis, NO is called an ‘endogenous anti-atherogenic molecule’. Any condition that will reduce endothelial NO production may therefore promote atherosclerosis.

Methylarginines have long been described as endogenous compounds present in human plasma [16,17]; however, at that time it was still unknown that they may interfere with a signal transduction pathway that is important for vascular biology. In contrast to ADMA, symmetric dimethylarginine (SDMA) does not act as an inhibitor of NO synthase (Fig. 2) [15,18].

Data from experimental studies suggest that ADMA inhibits vascular NO production at concentrations found in pathophysiological conditions (i.e., 3–15 μmol/l) [15,19–21]. In cultured murine macrophages, ADMA also inhibits NO production in a concentration-dependent manner [22,23]. Faraci et al. [20] calculated an IC\textsubscript{50} value of 1.8±0.1 μM for the inhibition of NO production in rat cerebellar homogenate by ADMA, and Fickling et al. [23] reported that 2 and 10 μM ADMA inhibited nitrite production in LPS-stimulated J774 macrophages by 17 and 33%, respectively.

In in vitro experiments with purified NO synthase (NOS) isoforms, Vallance et al. [15] reported that ADMA concentration-dependently inhibited macrophage NOS. We recently demonstrated that ADMA concentration-dependently inhibits endothelial (IC\textsubscript{50} =3.9 μmol/l) and neuronal NO synthase activities [24].

Uncoupling of NOS catalytic activity has been observed under experimental conditions in which NOS is unable to catalyze the two-electron oxidation of l-arginine to nitric oxide, either in the presence of a suboptimal l-arginine concentration [25], or when the enzyme is depleted of essential co-factors such as tetrahydrobiopterin [26]. A similar shift in eNOS catalytic activity is observed in the...
presence of l-NMMA or LDL cholesterol [27]. Under such conditions, optimal electron flow within the two catalytic domains of NOS is impaired and molecular oxygen becomes the sole electron acceptor, rendering NOS into a generator of superoxide radicals (‘uncoupling of NOS activity’; Fig. 3) [25–27]. We have reported earlier that ADMA concentration-dependently increases superoxide production by cultured human endothelial cells, causing activation of redox-regulated transcription factors such as NF-κB and concomitant up-regulation of endothelial adhesion molecules and monocyte adhesion [18]. This finding supports the hypothesis that ADMA, like l-NMMA, uncouples NOS activity (Fig. 3). Further experiments are warranted to verify this hypothesis.

![Chemical structures of l-arginine, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA). l-Arginine is the natural substrate for NO synthase, ADMA is a competitive inhibitor of NO synthase, whereas SDMA is biologically inactive.](image)

Fig. 2. Chemical structures of l-arginine, asymmetric dimethylarginine (ADMA), and symmetric dimethylarginine (SDMA). l-Arginine is the natural substrate for NO synthase, ADMA is a competitive inhibitor of NO synthase, whereas SDMA is biologically inactive.

![Fig. 3. NO synthase is a dimer formed by an oxygenase and a reductase domain. Under ideal catalytic conditions (i.e., in the presence of optimal concentrations of the substrate l-arginine and co-factors (tetrahydrobiopterin (BH4), calmodulin (CaM), NADPH, FMN, and FAD), electron transfer (e−) occurs from molecular oxygen along the cascade of co-factors to l-arginine (A). NO and l-citrulline are the products of this reaction. Under suboptimal conditions (e.g., relative l-arginine deficiency, in the presence of LDL cholesterol or l-NMMA) the catalytic mechanism is ‘uncoupled’ (B). Normal electron flow is perturbed, and molecular oxygen acts as an electron acceptor, resulting in the formation of superoxide radicals (O2−). Relative l-arginine deficiency can also be the result of elevated levels of the competitive NOS inhibitor, ADMA. Additional experimental evidence is required to ascertain whether an elevated ADMA concentration also leads to uncoupling of NO synthase, as hypothesized in this figure.](image)

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3. Biosynthesis, metabolism, and excretion of ADMA

3.1. Biosynthesis

The biochemical and physiological pathways related to ADMA are summarized in Fig. 4. Dimethylarginines are the result of the degradation of methylated proteins [17,28]. S-Adenosylmethionine:protein arginine N-methyltransferases (protein methylases I and II) have been shown to methylate internal arginine residues in a variety of polypeptides, yielding \( N^\omega \)-monomethyl-L-arginine and \( N^\omega,N^\omega \)-dimethyl-L-arginine (ADMA; protein methylase I), or \( N^\omega \)-monomethyl-L-arginine and \( N^\omega,N^\omega \)-dimethyl-L-arginine (SDMA; protein methylase II) [29]. Free ADMA and SDMA are released during proteolytic breakdown.

The methyl groups contained within the dimethylarginine molecules are derived from S-adenosylmethionine as a methyl group donor. Upon incubation of endothelial cells with S-\([1^\text{C}]\)-adenosylmethionine, the radioactively labeled tracer is recovered in part within the fraction coeluting with ADMA, but not with SDMA, in HPLC analysis [30]. In the presence of native LDL, methyltransferase activity is increased by about three-fold, which may be due, in part, to upregulation of N-methyltransferase gene expression [30]. Proteolysis is necessary to release free methylarginine residues, which makes it likely that, although protein arginine methylation is involved in the increased production of ADMA and SDMA, it may not be the decisive step in the fine regulation of their free concentrations.

Cultured human endothelial cells are capable of synthesizing ADMA and SDMA [23,28,30–32]. ADMA likely acts as an autocrine regulator of endothelial NO synthase activity under certain conditions. We found that the release of ADMA into conditioned media of endothelial cells incubated in the presence of native or oxidized LDL is increased as compared to control conditions [18]. These data indicated that low-density lipoprotein increases endothelial cell ADMA formation by a mechanism not yet elucidated in detail. Ito et al. [33] showed that incubation of cultured human endothelial cells with oxidized LDL or TNF-\( \alpha \) also increased the level of ADMA in the conditioned medium.

The ADMA levels in lysed endothelial cells were about eight- to 12-fold higher than those in conditioned media [18], amounting to 8–40 \( \mu \)mol/l. Bogle et al. [34] also found elevated dimethylarginine levels in cytoplasm as compared to the extracellular fluid, and demonstrated competition of L-arginine and dimethylarginines for the cellular uptake mechanism (\( \gamma^+ \)-transporter). A similar finding was reported by Azuma et al. [31], who measured ADMA levels in healthy and in regenerated endothelium.
after experimental balloon angioplasty. They found that regenerated endothelial cells produced more ADMA than control cells. In either case, intracellular ADMA levels in harvested endothelial cells were significantly higher than those determined in plasma of the same animals.

3.2. Renal elimination

Both ADMA and SDMA are eliminated from the body by renal excretion. The initial paper by Vallance et al. [15] reported higher mean ADMA and SDMA plasma levels in nine patients with end-stage renal disease (8.7±0.7 μmol/l) than in six healthy controls (1.2±0.1 μmol/l). Subsequently, elevated plasma levels of ADMA and SDMA have been reported in larger cohorts of patients with renal failure by several groups, including our own. These data have been extensively reviewed [35]. Although the absolute concentrations varied between studies due to differences in analytical methods and in the patient populations studied, all studies reported a mean two- to 10-fold increase in ADMA and six- to nine-fold increase in SDMA concentration as compared to healthy controls [35,36]. However, there is evidence that dialytic clearance in patients with chronic renal failure undergoing hemodialysis is lower than predicted [36,37]. This has been related, in part, to protein binding of ADMA in human plasma. Moreover, different treatment methods may result in different levels of ADMA and SDMA. In hemodialysis patients, high levels of ADMA and SDMA are present, whereas high SDMA levels accompanied by low ADMA levels are found in plasma of patients undergoing peritoneal dialysis [36,37]. This may point to the fact that the kidney is the only elimination pathway for SDMA, whereas an alternate, metabolic pathway is involved in the elimination of ADMA [28]. Interestingly, Cross et al. [38] found that hemodialysis reduced ADMA levels and, concomitantly, improved endothelium-dependent vasodilation. By contrast, peritoneal dialysis, which did not reduce ADMA levels, did not improve endothelium-dependent vasodilation.

3.3. Metabolism by dimethylarginine dimethylaminohydrolase

The metabolism of ADMA, but not SDMA, occurs via hydrolytic degradation to citrulline and dimethylamine by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) [39]. Inhibition of DDAH causes gradual vasoconstriction of vascular segments, which is reversed by L-arginine [32]. This latter finding also suggests that regulation of intracellular ADMA levels by DDAH affects NO synthase activity. Two different isoforms of DDAH are known, DDAH-1 and DDAH-2. DDAH-1 is typically found in tissues expressing neuronal NOS, whereas DDAH-2 predominates in tissues containing the endothelial isoform of NOS [40]. More recently, the enzyme has been cloned, purified, and its tertiary structure identified by crystallography [41].

The activity of this enzyme appears to be subject to complex regulatory mechanisms, which are not yet understood in detail. Ito et al. [33] demonstrated that oxidative stress induced by oxLDL or TNF-α decreased DDAH activity, but not its protein expression, in cultured endothelial cells. Homocysteine also increased ADMA levels by reducing DDAH activity via a redox-mediated mechanism, and directly interfered with isolated DDAH in a cell-free system [42]. DDAH activity is inactivated by S-nitrosylation [43], suggesting the existence of a feedback regulatory mechanism by which high NO levels upregulate the levels of ADMA. Gene expression of DDAH is induced by all-trans-retinoic acid [44]. Further experimental studies are necessary to fully elucidate the regulation of gene expression and activity of this enzyme, as well as its role in health and disease.

Therefore, it is likely that ADMA is constantly being produced in the course of normal protein turnover, and that its accumulation is prevented by its metabolism by DDAH. Changes in DDAH activity may contribute to elevated ADMA levels in various diseases.

4. ADMA is a marker for endothelial dysfunction

The plasma concentration of ADMA is elevated in hypercholesterolemic rabbits [45]. This is a pathobiological change occurring very early in the development of plaques in this animal model. When rabbits are placed on a diet enriched with 1% cholesterol, ADMA levels are increased within 4 weeks of dietary intervention as compared to control animals [46]. ADMA also increased in plasma of humans with hypercholesterolemia or atherosclerosis. ADMA levels, which are 1.0±0.1 μmol/l in healthy humans, are elevated to 2.2±0.2 μmol/l in young, clinically asymptomatic hypercholesterolemic individuals [47]. In elderly patients with peripheral arterial disease and generalized atherosclerosis, we found ADMA levels ranging from 2.5 to 3.5 μmol/l, corresponding to the severity of the vascular disease [48]. Increased ADMA levels were associated with reduced NO production in hypercholesterolemic subjects and in atherosclerotic patients, as judged by reduced urinary nitrate excretion and impaired endothelium-dependent, NO-mediated forearm vasodilation [47,48]. Our conclusion from these studies was that ADMA is a risk factor for endothelial dysfunction. Elevated plasma concentrations of ADMA are also present in hypertensive patients [49], in patients with chronic heart failure [50], and in other patient groups (Table 1). Recent-
ly, a close relationship between ADMA and insulin resistance has been observed in apparently healthy humans [51].

5. Endothelial dysfunction is a prognostic marker for severe cardiovascular events

Endothelium-dependent vasodilation has been a much investigated phenomenon since Robert Furchgott’s initial observation in 1980 that the relaxation response of isolated arterial segments to acetylcholine is dependent upon the presence of intact endothelial cells [58]. Since then, myriads of studies have been performed to study the role of endothelium-dependent vasodilation and its major mediator, nitric oxide, in a variety of cardiovascular and metabolic diseases. These studies have been extensively reviewed [59,60]. Several prospective clinical trials have recently made clear that endothelial dysfunction indicates an increased cardiovascular risk. Schächinger et al. [61] assessed the coronary response to the intracoronary infusion of acetylcholine in 147 patients. After a mean 7.7 years of follow-up, 28 major cardiovascular events had been observed in 16 patients. The vast majority of these events had occurred in those patients whose coronaries had initially responded with vasoconstriction to acetylcholine (i.e., those with endothelial dysfunction). These authors concluded that impaired coronary endothelial vasodilation is associated with a significantly higher incidence of cardiovascular events during long-term follow-up. In another study, Suwaidi and colleagues [62] assessed the coronary vascular response to intracoronary acetylcholine infusion in 157 patients. After a mean 28 months of follow-up, a total of 10 cardiac events had occurred, all of which were observed in patients who had initially had severe endothelial dysfunction, whereas none of the patients with coronary vasodilation to acetylcholine experienced a cardiac event. Several other groups of investigators have confirmed these findings in other groups of patients.

6. ADMA is a risk factor for cardiovascular disease

Studies in animal models as well as in humans had suggested that the increase in ADMA occurs at a time when vascular disease has not yet become clinically evident. However, whether this conferred a causative relationship between elevated ADMA levels and vascular disease had remained unclear until recently.

Miyazaki et al. [63] measured dimethylarginine levels in the plasma of 116 human subjects who had no signs of coronary or peripheral arterial disease. They found that ADMA levels were positively correlated with age, mean arterial pressure, and glucose tolerance. Most intriguingly, ADMA levels were significantly correlated with carotid artery intima-media thickness in a stepwise regression analysis of this population. As the relationship between carotid intima-media thickness and major cardiovascular events had also recently been established [64,65], these authors proposed that ADMA is a marker of cardiovascular disease.

We performed three different trials to assess the relationship between ADMA and cardiovascular disease in patients with chronic renal failure. In the first study, we measured intima-media thickness by ultrasound in 90 patients undergoing chronic hemodialysis, and related the results to conventional risk factors as well as ADMA plasma concentration [66]. We found that ADMA was highly significantly correlated with intimal thickening in this population, which confirmed the results of Miyazaki et al. [63]. We then assessed the progression of the intima-media thickness during a period of 1 year, and found that ADMA and C-reactive protein levels emerged as the sole independent predictors of the progression of intimal lesions in patients with initially normal intima-media thickness [66].

In a second, larger prospective trial, we measured the ADMA concentration as well as a variety of conventional and new cardiovascular risk factors in 225 hemodialysis patients. After a mean 33.4 months of follow-up, 120 major cardiovascular events and a total of 83 deaths (53 vascular deaths) had occurred. In a Cox’s proportional-hazards model, ADMA and age were the strongest predictors of cardiovascular events and total mortality [55]. Although the median plasma ADMA concentration in this population (2.52 μmol/l) was higher than in healthy normal adults (=1 μmol/l), patients with an ADMA concentration above the 75th percentile within this group had a three-fold higher risk of death from any cause than patients with ADMA levels below the median (Fig. 5).

In the third study, we analyzed cardiac performance by echocardiography in 198 patients with end-stage renal failure. ADMA was significantly related to left-ventricular mass and inversely related to ejection fraction [67]. This relationship was stronger in patients with concentric hypertrophy of the left ventricle than in those with eccentric hypertrophy.
The relationship between ADMA concentration and cardiovascular events has been confirmed in a study by Valkonen et al. [68]. They showed in a prospective, nested case-control study that middle-aged men who did not smoke, but who had ADMA plasma levels in the highest quartile, had a 3.9-fold increased risk for acute coronary events compared with the other quartiles.

Our present knowledge concerning the relationship between ADMA, traditional risk factors, and cardiovascular disease may help to explain why some patients with traditional risk factors never experience cardiovascular events, while others without traditional risk factors do. Novel risk markers such as ADMA, which is elevated in a proportion of hypercholesterolemic patients but not in all of them [47], and may also be elevated in a proportion of apparently ‘normal’ subjects, may contribute to the pathogenesis of atherosclerotic disease.

Nijveldt and co-workers recently reported an interesting study in which they found that ADMA was the strongest predictor of death of patients in an intensive care unit, with a 17-fold excess in mortality for patients in the highest ADMA quartile as compared to those in the lowest quartile [69]. ADMA was significantly associated with hepatic failure, lactic acid, and bilirubin concentrations, suggesting that hepatic function is an important determinant of the circulating ADMA concentration.

At least three case-control studies are currently being undertaken to further assess the relationship between ADMA and cardiovascular risk in different populations. The results of these trials will further extend our understanding of this novel cardiovascular risk factor. Further, prospective trials are now warranted to prove the hypothesis that ADMA is a predictor of cardiovascular events and/or mortality, and thus to assess its suitability as a diagnostic marker of ischemic vascular disease.

7. Methodological aspects of assessing ADMA concentrations in human plasma and urine

In the light of accumulating data favoring a role for ADMA as a cardiovascular risk marker, diagnostic assays are needed that allow rapid and inexpensive quantification of this compound and that are ubiquitously available. Methods of quantitation that have been used so far comprise high-performance liquid chromatography with previous extraction of analytes from the plasma or urine matrix [15,47,70]. These methods are laborious and costly and are only available in specialized laboratories. However, most of these assays have conformed with the analytical requirements: specificity for ADMA without cross-reactivity with SDMA or L-NMMA; low detection limit to allow quantitation of ADMA in healthy subjects; high reproducibility of the results. We have recently developed an enzyme-linked immunosorbent assay (ELISA) for ADMA using a highly specific polyclonal antibody that has been validated against HPLC and confirmed using gas chromatography–mass spectrometry. The cross-reactivity of this antibody with SDMA and L-NMMA is below 5%. In a series of human serum samples, the correspondence between values determined by HPLC versus ELISA was excellent ($R^2 = 0.994$, $P<$...
0.0001). This novel assay allows the rapid, reproducible, and sensitive determination of ADMA, and it can be used ubiquitously, making it a useful tool for future studies on ADMA as a cardiovascular risk factor.

8. Testing pharmacotherapeutic interventions to reduce the effects of ADMA on vascular function

With our increasing knowledge of the role of ADMA in the pathogenesis of cardiovascular disease, ADMA is becoming a goal for pharmacotherapeutic interventions.

The observations that hyperglycemia [51] or hypertriglyceridemia [71] acutely elevate ADMA levels suggest that its concentration is tightly regulated by this activity, and not only by the expression of related enzymes. This makes it possible to develop strategies aimed at reducing the ADMA concentration in patients with cardiovascular disease. Our improved understanding of the catalytic mechanism and the structure of DDAH [41] makes this enzyme a primary goal in these efforts.

Ito and colleagues recently demonstrated that inhibitors of the renin–angiotensin system reduce elevated ADMA levels in patients with essential hypertension [72]. This observation was confirmed in another small study by Delles et al. [73] in which ADMA levels were significantly reduced during treatment with an ACE inhibitor and an angiotensin receptor blocker, respectively. Further data suggested that anti-oxidant substances [33] and anti-diabetic drugs such as metformin [74] and rosiglitazone [51] may also be among the pharmacological tools that are suitable for this purpose. A recent clinical study suggested that treatment of postmenopausal women with conjugated equine estrogen reduces ADMA levels by a mean 7.8% [75]. Whether this was due to an effect of estrogen on DDAH activity and/or expression remains to be determined. In another study, treatment with folic acid lowered ADMA plasma levels in hyperhomocysteinemic subjects [76]. This finding was in contrast to our observation that combined treatment with folic acid, vitamin B6 and B12 did not change the plasma ADMA concentration in elderly subjects with hyperhomocysteinemia and vascular disease [77]. Whether reversal of elevated ADMA levels will be of benefit with regard to clinical symptoms of patients remains to be elucidated in future trials.

One possibility to counteract the adverse effects of ADMA on the vasculature that has been tested in a broad range of clinical trials is by reversing its competitive inhibition of NOS by exogenous L-arginine. Administration of L-arginine has been shown not only to improve endothelium-dependent vascular function in subjects with high ADMA levels [47,78], but also to improve the clinical status of patients with cardiovascular disease in some studies [54,79–81], but not in all [82,83]. Competition of supplemental L-arginine with endogenous ADMA for NOS in those patients with elevated ADMA levels, but not in those with ADMA within the ‘normal range’ (which remains to be determined), may be an explanation for why, in the past, some authors have reported beneficial effects of L-arginine supplementation while others found no positive effect of this treatment [84].

9. Conclusions and outlook

It has been 10 years since ADMA was first described as an endogenous inhibitor of NO synthase in human plasma and urine. Since that time, we have gained a detailed understanding of the biosynthesis and metabolism of ADMA, and we have learned about its role in determining endothelium-dependent vasodilation in several diseases. Recent clinical studies have added interesting data suggesting that ADMA might be a novel cardiovascular risk factor, allowing the prospective identification of patients at high risk of developing cardiovascular disease or death—beyond the ability of currently existing risk scores. Future studies will have to focus on prospective studies in different patient populations to further characterize the role of ADMA as a risk factor, and on pharmacotherapeutic intervention trials aiming at reducing the influence of ADMA on the vascular endothelium.

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