


The Role of ADMA in Various Diseases

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ABSTRACT

Asymmetric dimethylarginine (ADMA) is a competitive inhibitor of nitric oxide synthase (NOS). Numerous studies have discovered a correlation between high plasma ADMA levels and the development of multiple diseases, including cardiovascular disease, chronic renal disease, diabetes mellitus, liver diseases, preeclampsia, and COVID-19. In addition, ADMA has been established as an independent cardiovascular risk factor. However, the functional interplay between ADMA and nitric oxide (NO)-mediated pathways is poorly understood, leaving the distinction between "risk factor" and "risk marker" unclear. In this review, we provide insights into the current state of knowledge regarding the pathophysiological role of ADMA in various diseases, the relationship between ADMA and endothelial dysfunction, the current analytical techniques used to determine ADMA in body fluids, and the benefits of ADMA-lowering drugs for the prevention of diseases in humans.

Keywords: ADMA, cardiovascular disorders, nitric oxide, risk marker

ABSTRAK

Asymmetric dimethylarginine (ADMA) adalah penghambat kompetitif *nitric oxide synthase* (NOS). Banyak penelitian menemukan hubungan antara peningkatan kadar plasma ADMA dan perkembangan berbagai penyakit, termasuk penyakit kardiovaskular, penyakit ginjal kronik, diabetes melitus, penyakit hati, preeklampsia, dan COVID-19. ADMA juga diidentifikasi sebagai faktor risiko independen untuk penyakit kardiovaskular. Namun, interaksi fungsional antara ADMA dan *nitric oxide* (NO) belum begitu dipahami, yang menyebabkan tidak jelasnya batasan antara "faktor risiko" dan "penanda risiko". Tulisan ini membahas pengetahuan terbaru tentang peran patofisiologi ADMA dalam berbagai penyakit, hubungan antara ADMA dan disfungsi endotelial, teknik analisis terkini untuk pemeriksaan kadar ADMA dalam cairan tubuh, serta manfaat obat penurun ADMA untuk pencegahan penyakit pada manusia. **Sofna Banjarnahor, Reny Damayanti. Peran ADMA pada Berbagai Penyakit.**

Kata kunci: ADMA, penyakit kardiovaskular, *nitric oxide,* penanda risiko

INTRODUCTION

The accumulation of asymmetric dimethylarginine (ADMA) has been related to several vascular diseases. Vallance, *et al*, were the first to suggest that ADMA may have a pathophysiological role as a competitive inhibitor of nitric oxide synthase (NOS). In addition, they found an increase in methylarginine in the plasma of patients with end-stage renal failure.[1] Since then, ADMA has been discovered as an independent risk factor for cardiovascular events.[2] ADMA meets several criteria for a uremic toxin: it accumulates when the kidney fails, is a byproduct of protein metabolism, is a guanidino compound, and has the potential to affect numerous biological pathways disrupted in patients with chronic renal failure, such as the cardiovascular system, bone, and immune system.[1]

Given the clinical importance of ADMA on vascular (i.e., endothelial) health, three studying ADMA metabolism, particularly its transport and clearance pathways, may provide a complete picture of how this metabolite exerts its harmful effects. Consequently, this study aims to provide clinicians with knowledge on ADMA and, where available, research linking ADMA to human diseases. The following section briefly outlines how ADMA is examined and if it may be utilized in clinical practice. Most importantly, lowering ADMA in individuals with ADMA-related diseases has benefits.

ADMA Metabolism and Transport

In 1970, Kakimoto and Akazawa isolated and characterized ADMA in human urine.[4] They stated that ADMA was formed endogenously and was unaffected by diet. Using high-performance liquid chromatography (HPLC),[5] ADMA may be quantified in human plasma.[6] Protein arginine N-methyl-transferases (PRMT) generate ADMA by methylating protein-bound L-arginine post-translationally.[7]

ADMA is produced when PRMT methylates the guanidine group of L-arginine. Both types of PRMT catalyze the monomethylation of L-arginine to NG-monomethyl arginine (NMMA).[7] Attachment of the second methyl group by PRMT types 1 or 2 generates different product-asymmetric (ADMA) and symmetric dimethylarginine (SDMA) - respectively.

Most ADMA is either degraded in the cytoplasm of the cell that made it or eliminated through the kidneys. Due to its physical features, ADMA, like other cationic amino acids, requires specific transport systems known as amino acid transporters. Two methods are known to transport cationic amino acids: y+ and y+L.

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The y+ system, known as cationic amino acid transporters (CATs), can transport ADMA and its analog molecule, L-arginine, across the cell membrane[8] and to other cells.[9] Whereas the y+L system transports neutral and cationic amino acids.[10]

ADMA clearance by the kidney is mediated through the action of dimethylarginine dimethylaminohydrolases (DDAHs).[11] This enzymatic family in higher organisms consists of two isoforms encoded by genes on chromosomes 1 (DDAH-1) and 6 (DDAH-2), with distinct tissue-specific distributions but seemingly similar activities.[12] In addition, subsequent research has implicated the liver in the metabolism of dimethylarginines. Researchers have demonstrated that hepatocyte membranes contained abundant y+ channels[13] and high concentrations of DDAH.[14] A recent study on patients undergoing hepatectomy confirmed the presence of ADMA in the liver.[15] These metabolic studies have shown that the liver is essential for regulating plasma dimethylarginine concentrations.

CLINICAL OVERVIEW

The plasma concentration of ADMA in healthy adults ranges between 0.4 M and 1 M;[16] it can increase to between 1.45 M and 4.0 M in some diseases. Given the growing understanding of the roles of ADMA in the pathogenesis of conditions, the following part focuses on disorders associated with elevated plasma levels of ADMA.

ADMA in Cardiovascular Diseases

Numerous investigations have established a strong correlation between increased ADMA levels and cardiovascular diseases. Kielstein, *et al*, observed that patients with hypertension had greater plasma levels of ADMA than normal-tension individuals.[17] Elevated plasma ADMA levels have also been found in hypertensive youngsters.[18] In addition, Wang, *et al*,[19] and Surdacki, *et al*,[20] reported elevated plasma levels of ADMA in newly diagnosed and treated hypertension patients. In addition, high plasma ADMA in individuals with myocardial infarction or chronic left heart failure is one of the strongest predictors of mortality.[9]

ADMA levels are elevated in patients with heart failure,[21-23] and it has been demonstrated that ADMA reduces ventricular contraction and heart rate.[24] According to Kielstein, *et al*,[25] exogenous ADMA increases systemic vascular resistance and mean arterial pressure while lowering cardiac output in the male group. In addition, they observed that ADMA infusion decreased renal circulation and salt reabsorption related to dosage. ADMA may contribute to the pathogenesis of cardiovascular diseases via two distinct mechanisms. On the one hand, ADMA inhibits endothelial nitric oxide synthase (eNOS) activity, resulting in vasoconstriction of blood vessels.[24,26] On the other hand, ADMA suppresses nitric oxide (NO) synthesis in the kidneys, resulting in reduced salt excretion.[27-29]

ADMA in Chronic Kidney Diseases

High ADMA levels have also been found in human patients with kidney diseases and have been identified as a predictive factor in chronic kidney disease (CKD) patients.[30] Vallance, *et al*, were the first to show increased plasma levels of ADMA in CKD patients.[1] A recent meta-analysis of 18 studies with a total of 2136 patients with varying stages of renal failure revealed that plasma concentrations of ADMA were up to 3.4 times higher in renal insufficiency patients on dialysis compared to healthy control groups.[31] However, it is doubtful whether the elevated ADMA levels result from a pathogenic process or an inflammatory byproduct.

According to reports, the kidney is the primary organ responsible for ADMA elimination.[32] The greatest expression and activity of the ADMA breakdown enzyme DDAH[1] is found in the kidneys.[33] ADMA accumulation can occur from reduced DDAH1 activity[34,35] via enhanced DDAH[1] degradation by post-translational modifications such as DDAH[1] protein oxidation[36,37] or DDAH[1] gene loss-of-function mutations.[38] Therefore, if the kidney fails, ADMA will accumulate, making it a predictor for renal failure. Increased ADMA, on the other hand, may affect various renal functions, such as tubuloglomerular feedback (TGF) response, tubular sodium and proton transport, and renal sympathetic nerve activity,[39] making ADMA a causative factor of kidney diseases.

ADMA in Diabetes Mellitus

High levels of plasma ADMA are also found in diabetic patients who develop microvascular complications in the retina,[40] nerves,[41] and kidneys.[42] A meta-analysis found that ADMA might have a role in the genesis of diabetic microvascular complications.[43] Lin, *et al*, observed a correlation between diabetic rat DDAH activity and ADMA levels.[37] When human endothelial cells (HMEC-1) and vascular smooth muscle cells were exposed to a high-glucose medium, DDAH activity was significantly reduced. Hyperglycemia-induced oxidative stress leads to ADMA accumulation, which may contribute to endothelial vasodilator dysfunction resulting from insufficient NO production. In addition, Lee, *et al*, demonstrated in a cross-sectional study that increased ADMA concentrations may also inhibit insulin-stimulated glucose absorption in skeletal muscle by altering insulin signaling.[44] Furthermore, they stated that ADMA was pathophysiologically significant as a potential biomarker of insulin resistance in skeletal muscle. Whether ADMA accumulation affects insulin signaling and insulin resistance in humans must be determined. These results reveal the possibility of a novel therapeutic target with clinical relevance for regulating energy and metabolic balance.

ADMA in Liver Diseases

Plasma ADMA concentrations have increased in individuals with hepatic impairment.[45] Notably, plasma ADMA levels are strongly correlated with the severity of hepatic dysfunction in patients with liver diseases of diverse etiologies.[46,47] Individuals with alcoholic hepatitis,[48] liver cirrhosis, [49] and acute liver failure have elevated plasma ADMA levels.[45] Plasma ADMA levels are associated with hepatic impairment in cirrhosis and are much higher in individuals with decompensated cirrhosis than in those with compensated cirrhosis.[48] Due to the increased expression of the ADMA-degrading enzyme DDAH in the liver, the liver plays an indispensable role in ADMA elimination. Animal studies have indicated a negative correlation between serum ADMA concentrations and liver DDAH activity.[50] The significance of ADMA in liver disease is tied to its ability to induce hepatic malperfusion. Loss of liver function interferes with DDAH activity and the subsequent clearance of ADMA, resulting in a considerable rise in plasma ADMA levels and inhibition of NO generation, reducing hepatic flow and affecting other organs.[47]


ADMA in Preeclampsia

Elevated ADMA levels in women with preeclamptic pregnancy have been demonstrated in many studies.[51, 52] Plasma ADMA levels are increased when measured at the 23-25th week of pregnancy, even before the onset of preeclampsia,[53] similar to what Speer and colleagues found in their studies.[54] Pettersson, *et al*,[55] showed that plasma ADMA was higher in third-trimester preeclamptic patients (0.55 ± 0.02 mmol/l; $p<0.05$) compared to normotensive pregnant controls (0.36 ± 0.01 mmol/l) of the same gestational length. A substantial difference was also observed between preeclamptic and normal pregnant women. In contrast, extensive studies involving Colombian women showed no significant difference in ADMA levels between normal pregnancy and preeclamptic pregnancy.[56] It has been suggested that the relative cardiovascular and infectious risk of a community may explain this leveling of ADMA-associated risk.[52]

Whether ADMA has a role in normal pregnancies remains undetermined. Maeda, *et al*,[57] discovered that maternal concentrations of ADMA were lower in normal pregnancies than in non-pregnant women, indicating that ADMA is essential for vasodilation during pregnancy. Recently, Saarelainen, *et al*,[58] have cast doubt on the role of ADMA as a critical regulator of blood pressure in normal pregnancy. Their study demonstrated only subtle alterations of ADMA and no correlation between endothelium-dependent vasodilatation markers and maternal serum concentrations of ADMA or L-arginine. Similarly, Braekke, *et al*, found that maternal concentrations of ADMA and L-arginine were significantly higher in preeclamptic women than in healthy controls. They suggested that the effect of ADMA on NOS could be attenuated by high L-arginine, which obscures the previous suggestion of ADMA as a predominant factor of endothelial function in preeclampsia.[59]

Interestingly, ADMA levels are elevated even before preeclampsia onset[53,54] suggesting that ADMA could play a role in the development of preeclampsia and offers a potential role for ADMA as a novel risk marker for the early detection of high-risk pregnancy. These results suggest that ADMA influences preeclampsia via a complex mechanism. ADMA may be elevated due to an excess of methylated arginine residues on proteins, the metabolism of ADMA by DDAH may be impaired, or elevated ADMA may come from underlying changes in renal function.

ADMA in COVID-19

Hanemann, *et al*, initially found a correlation between elevated plasma levels of ADMA and COVID-19 severity. They observed that ADMA might be used to identify hospitalized COVID-19 patients with a high probability of hospital mortality.[60] It is unknown how ADMA contributes to the pathophysiology of COVID-19, but decreased nitric oxide (NO) production by endothelial cells may play a role in COVID-19-associated morbidities. Impaired NO production may interfere with two key pathophysiological processes: vascular dysfunction and immune function.[61]

Endothelial cells infected with the SARS-CoV-2 virus develop endotheliopathy,[62] perhaps resulting in endothelial dysfunction and NO deficiency due to cell tropism. According to Ueda, *et al*,[63] the ADMA-DDAH system regulates inflammation-mediated NO production via inducible NOS (iNOS). Expression of the third isoform, iNOS, is dependent on inflammatory mediators (i.e., cytokines, bacterial lipopolysaccharide, and interferons)[64] and virus infection,[65] and other pathophysiological stimuli.[66, 67]

Upon induction, iNOS can produce 1,000 times more NO than eNOS and persist until the enzyme is destroyed, which can take several hours due to the tight interaction between calmodulin and the enzyme.[68] iNOS-derived NO can lead to harmful effects not due to the direct actions of NO, but rather due to the abundance of NO available to react with superoxide radical (O_2^-), leading to the formation of the highly reactive (and harmful) radical, peroxynitrite ($ONOO^-$), and further downstream, derivatives such as nitryl and hydroxyl peroxide.[69] These harmful effects have been linked to several human illnesses,[70] including COVID-19.[62] A study demonstrated that plasma nitric oxide (NO) species were lower in COVID-19 patients than in healthy controls due to a decreased production or increased consumption of reactive oxygen species scavenging.[71] Others have recommended monitoring nitrite/nitrate levels (NOx) and even supplementing COVID-19 with exogenous nitrate or nitrite.[72] Therefore, inflammation-induced oxidative stress, as seen in COVID-19, modifies the activity of the redox-sensitive ADMA-related enzymes PRMT and DDAH.[73] As a result, plasma ADMA levels increase, boosts the inhibition of eNOS and iNOS, and worsens the clinical condition.

ADMA-mediated Endothelial Dysfunction

The endothelium is essential for maintaining vascular tone and structure. Endothelial dysfunction is associated with cardiovascular, metabolic, and systemic or local inflammation risk factors.[74] Elevated blood levels of ADMA, an analog of the amino acid L-arginine, is one proposed mechanism for developing endothelial dysfunction.[75]

As noted above, ADMA inhibits all three NOS isoforms for the formation of nitric oxide,[1] the most potent endogenous vasodilator and a critical signaling molecule for numerous molecular targets.[76] A high concentration of ADMA could therefore impair vascular function. ADMA causes an increase in renal vascular resistance and blood pressure in rats.[77] Additionally, local intraarterial infusion of ADMA has been reported to reduce forearm blood flow significantly.[78] Moreover, intravenous infusion of ADMA increased mean blood pressure by 6 percent and systemic vascular resistance by 24 percent while reducing the effect of exercise on cardiac output (by 15 percent), heart rate, and vascular responsiveness.[24] These findings confirm its biological action *in vivo*.

Some have argued, however, that the concentration of ADMA in plasma, even in disease states, is too low to inhibit NOS effectively and that the average concentrations of L-arginine in cells should counteract the inhibitory effects of ADMA on NOS.[79] It should be highlighted that the interaction of ADMA with eNOS should be more comprehensive than just ADMA levels alone. Other cellular processes, such as those involving the transport and metabolism of ADMA and L-arginine, may be involved since L-arginine shares the same transporter with ADMA and is also the sole substrate for NO generation.[80]

ADMA Measurement

It has been demonstrated that ADMA concentrations in the general population fall within a restricted range.[81] Even when slightly increased, ADMA is associated with considerable cardiovascular risk.[82] Consequently, accurate

testing is necessary. Several variables regulate ADMA plasma concentrations; age,[83] race,[84] and body mass are among these determinants.[84] The measurement method is an additional crucial element influencing the concentration of ADMA.[83] Numerous analytical techniques for measuring ADMA in plasma and urine have been described. Among them are the enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography (HP-LC) with fluorescence detection, capillary electrophoresis, liquid chromatography coupled to mass spectrometry (LC-MS), and gas chromatography coupled to mass spectrometry (GC-MS).[85]

Each technique has its advantages and disadvantages. The most critical aspect of ELISA is that it is helpful in both routine diagnostic practice and clinical investigations. It is also very efficient and sensitive because it only measures one analyte simultaneously. However, compared to HPLC and MS-based methods, it has lower sensitivity for detecting ADMA in circulation.[86] The reduction in analysis time from a few hours to 30 to 60 minutes is a significant advantage of HPLC over other techniques. This method can also detect ADMA in biological fluid samples such as cell culture samples, tissue extracts, urine, plasma, and serum.[86] HPLC is now the most widely used method.[85] The HPLC-based method, on the other hand, cannot distinguish between ADMA and its structural analogs, such as symmetric dimethylarginine (SDMA) and L-arginine.[87] Mass spectrometry (MS)-based procedures provide a more precise determination of ADMA.[88] However, these methods require prohibitively expensive equipment for some facilities. Despite being established as a cardiovascular risk marker, plasma ADMA measurement is not yet standard in clinical practice.

ADMA-lowering Drugs

Is ADMA reduction beneficial? Extensive investigations have established causal links between ADMA and vascular function,[75] highlighting the potential advantages of a particular ADMA-reducing drug. No medications are currently available for ADMA-lowering treatment. The experimental data reveal that PRMT1, DDAH2, and CAT1 transporter modulate ADMA's intracellular and circulation amounts.[89]

At least three potential targets for treatments in ADMA-mediated vascular disease are theorized to exist. The first option is to inhibit PRMT1 specifically. However, creating a selective inhibitor for PRMT1, an enzyme with significant sequence conservation during evolution, is difficult.[90] In addition, as PRMT is implicated in complicated cellular physiology, PRMT1 inhibition might be a scam with adverse side effects.[91] Nonetheless, and several potent PRMT inhibitors require more experimental confirmation.[92]

Second, recent advancements in understanding the control of DDAH activity may yield significant new therapeutic opportunities.[33] Compounds, such as aminoguanidine,[93] pioglitazone,[94] pravastatin,[95] probucol,[96] farnesoid X receptor agonists,[97] melatonin,[98] and vitamin E[99] have been found as potentially therapeutically significant stimulants of DDAH enzyme activity and expression, hence lowering ADMA levels. Recently, a small molecule developed by modifying DDAH with polyethyleneglycol (PEG)ylation reduced blood pressure and improved renal function through lowering ADMA levels in animal models.[100] However, more examination is required before these "bench" results may be effectively translated to the "bedside."

ADMA buildup can be altered by inhibiting ADMA transport mediated by CAT1.[101] Recent *in vitro* investigations of the effects of some commonly prescribed medicines have indicated that some of these substances interfere with ADMA transport,[102] possibly changing extracellular and intracellular ADMA concentrations. However, it remains uncertain whether ADMA reduction treatment research conducted *in vitro* can be applied to humans. In addition, clinical research has investigated the impact of statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, metformin, hormone replacement therapy, fenofibrate, folate, and α-lipoic acid on the lowering of plasma ADMA levels.[103-106] However, it is still debatable whether a 20% drop in plasma ADMA levels generated by these medicines is beneficial in treating various disorders.

CONCLUSION

After over 30 years of research, ADMA is becoming a therapeutically functional metabolite. Despite this, several crucial ADMA concerns still need to be addressed. Because ADMA is processed by endothelial cells, a rise in ADMA may be the outcome of endothelial dysfunction rather than its cause. Although the exact reason for higher ADMA levels in diseases is unknown, the outlined scenarios can explain the rise. Increased PRMT-mediated ADMA synthesis in response to stress; increased breakdown or protein turnover, including methylated arginine; decreased ADMA degradation due to decreased DDAH activity, or decreased ADMA excretion as a result of renal dysfunction. Improved ADMA detection methods that permit routine clinical sample analysis would greatly assist future research. It is strongly desired that further study be conducted on its relevance as a causal factor and treatment development target. Hence, more research has to be focused on ADMA to reach clinical applications.

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