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Review Article

Asymmetric Dimethylarginine an Important Inflammatory Biomarker in Intensive Care Patients

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Abstract

Asymmetric dimethylarginine (ADMA), a naturally occurring guanidino-substituted counterpart of the conditionally essential amino acid arginine, is a metabolic by-product of ongoing protein turnover processes in the cytoplasm of all human cells. Dimethylarginines are produced when methylated proteins are broken down. There is evidence that alterations in cellular levels are brought on by pathophysiology and that cells create ADMA. Following balloon denudation, endothelial cells that repopulate blood vessels contained increased levels of ADMA. To ascertain the plasma levels of ADMA, numerous cardiovascular and other illnesses have been investigated. Elevated ADMA levels and, subsequently, the arginine-nitric oxide pathway, have been associated to critical illness. It has been established that individuals who are severely ill are exposed to elevated serum levels of ADMA.

Keywords: *Asymmetric Dimethylarginine; Metabolism; Critical Care; Cardiovascular*

Introduction

A metabolic by-product of on-going protein turnover processes in the cytoplasm of all human cells, asymmetric dimethylarginine (ADMA) is a naturally occurring guanidino-substituted analogue of the conditionally necessary amino acid arginine. Nitric oxide, a crucial regulator of the immune system and organ circulation, is made from arginine. Nitric oxide's bioavailability may be hampered by ADMA, an endogenous inhibitor of the enzyme nitric oxide synthase (NOS), which produces it [1].

Biosynthesis

Degradation of methylated proteins yields dimethylarginines [2]. The enzymes protein arginine methyltransferase type 1 and type 2 (PRMT1, PRMT2) are involved in the process of deriving the methyl groups from S-adenosylmethionine. While PRMT-2 methylates proteins to release NG, NG-dimethyl-L-arginine (symmetric dimethyl-arginine; SDMA), and L-NMMA, PRMT-1 catalyses the production of NG-monomethyl-L-arginine (LNMMA) and NG, NG-dimethyl-L-arginine (ADMA) [3,4]. The nitric oxide synthases are competitively inhibited by the asymmetrically methylated arginine residues (L-NMMA and ADMA), but not by symmetrically methylated arginine (SDMA). In the

presence of native or oxidised LDL, endothelial cells release more ADMA, which may be caused by an up-regulation of S-adenosylmethionine dependent methyl transferases [5] (Figure 1). Additionally, according to some evidence, the lung appears to have significant amounts of protein-bound ADMA as a result of the lung tissue's highly expressed levels of several PRMTs [6].

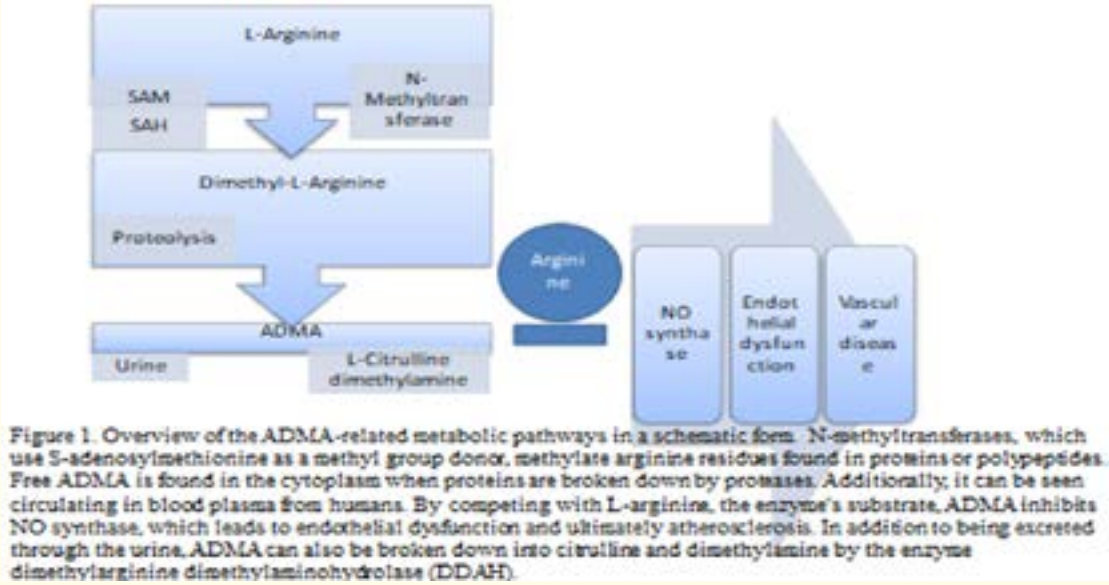

Figure 1. Overview of the ADMA-related metabolic pathways in a schematic form. N-methyltransferases, which use S-adenosylmethionine as a methyl group donor, methylate arginine residues found in proteins or polypeptides. Free ADMA is found in the cytoplasm when proteins are broken down by proteases. Additionally, it can be seen circulating in blood plasma from humans. By competing with L-arginine, the enzyme's substrate, ADMA inhibits NO synthase, which leads to endothelial dysfunction and ultimately atherosclerosis. In addition to being excreted through the urine, ADMA can also be broken down into citrulline and dimethylamine by the enzyme dimethylarginine dimethylaminohydrolase (DDAH).

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Metabolism and excretion

Endogenous ADMA and SDMA are eliminated in part by renal excretion. It has been demonstrated that SDMA excretion in the urine of rabbits is 30 times more than that of L-NMMA or ADMA [2]. Increased levels of ADMA and SDMA have been observed in studies of individuals with renal failure [7,8]. Unexpectedly, haemodialysis results in a lesser clearance of ADMA than anticipated, indicating that there may be additional non-renal routes for removing circulating ADMA [9].

The NG dimethylarginine dimethylaminohydrolase enzyme is responsible for the particular metabolic pathway for ADMA but not SDMA, which involves hydrolytic breakdown to citrulline and dimethylamine (DDAH) [10] (Figure 1).

The immune system also expresses DDAH in neutrophils and macrophages, as well as the kidney, pancreas, liver, brain, and aorta [11,12]. L-arginine can restore the progressive vasoconstriction that results from DDAH inhibition [13]. DDAH comes in two different isoforms, DDAH-1 and DDAH-2. While DDAH-2 is primarily present in tissues expressing the endothelial isoform of NOS, DDAH-1 is typically detected in tissues expressing neuronal NOS [14]. Decreased levels of DDAH are related to higher plasma concentrations of glucose, oxidised LDL, and homocysteine. Additionally, by causing increased oxidative stress, some traditional cardiovascular risk factors may

decrease DDAH function [15-18]. Increased ADMA concentrations and decreased NO generation are caused by pharmacological suppression of DDAH [19].

On the other hand, transgenic DDAH overexpression raises NO levels while lowering ADMA levels [20]. In studies on animals, it was discovered that DDAH overexpression inhibited myocardial reperfusion injury, ADMA-induced endothelial dysfunction in the cerebral circulation, and promoted endothelial repair after vascular injury [21-23]. It's interesting to note that selective silence of various DDAH isoforms has quite different biological effects from overexpressing DDAH-1 and DDAH2, which appear to have very similar phenotypic changes [24]. As a result, silencing of DDAH-1 led to an increase in circulating ADMA levels without affecting endothelium-mediated vasodilation, whereas silencing of DDAH-2 led to a marked reduction in endothelium-mediated vasodilation without a corresponding change in plasma ADMA concentration. This result is consistent with the observation that DDAH-2 is the isoform that is most prevalent in endothelium, whereas DDAH-1 is expressed at high levels in the kidneys and liver.

Cellular ADMA

Cells produce ADMA, and there is evidence that pathophysiology causes changes in cellular levels. In contrast to control cells, endothelial cells that repopulate blood arteries following balloon denudation had higher amounts of ADMA [25-28]. Endothelial cells concentrate methylarginines so that when methylarginines are given to culture medium, the concentrations in the cell increase to about 5-fold greater than in the surrounding medium, even if the precise concentration of ADMA within cells is unknown. This quantity of methylarginines is likely due to transport by the Y+ transporter, an arginine transport mechanism [29]. The observation that the Km of DDAH for ADMA is rather high (above 100 μmol/L) might imply that ADMA levels reach very high local concentrations under certain circumstances. However, it is not yet clear whether there is any compartmentalization of ADMA that might lead to pockets of very high concentrations. Both PRMTs and DDAHs are expressed by endothelial cells, and inhibiting DDAH causes ADMA to accumulate significantly [30-32]. Furthermore, functional research in vascular rings suggests that inhibiting DDAH results in alterations to endothelial functions that are consistent with high levels of ADMA near eNOS. A balance between the rates of arginine methylation, the breakdown of proteins containing methylated arginine, the metabolism of ADMA by DDAHs, and the rates of active extrusion from the cell is likely what determines the overall output of ADMA from endothelial cells. Since DDAH has a high metabolic capacity, it appears likely that DDAH activity will typically be the main predictor of overall ADMA levels within a cell, the proportional importance of each component is not yet understood.

The process of creating ADMA is intriguing, but it appears to be a laborious way to create a regulatory mediator. In fact, it is reasonable to anticipate that free methylarginine synthesis rates will remain stable. It is still unknown how protein turnover rates relate to ADMA production and whether ADMA is merely an "unlucky" by-product of protein degradation that must be removed by DDAH before it causes issues or if there is a significant biological connection between the NO pathway and the breakdown of specific types of proteins.

ADMA can diffuse between cells and is generally stable. Of fact, the NOS in a different type of cell can be inhibited by the ADMA produced in one cell [33]. This contact between macrophages and endothelial cells has been well documented, and it is conceivable that it will also happen between smooth muscle cells and endothelial cells. This suggests that ADMA might offer a signalling pathway for smooth muscle cells to communicate with the endothelium.

Circulating ADMA

Numerous cardiovascular and other disorders have been studied to determine the plasma levels of ADMA [34,35]. It is likely not unexpected that ADMA and SDMA concentrations rise in patients with renal failure because the kidneys are one pathway for the elimination of methylarginines [36-38]. The SDMA rises in accordance with creatinine and reaches values that are higher than the ADMA. This is not

unexpected considering that SDMA is not metabolised by DDAH but ADMA is. In other circumstances, SDMA appears to remain constant while ADMA is selectively enhanced [39]. This pattern of growth strongly points to DDAH dysfunction (Figure 2). It is unclear if the plasma concentration is merely a sign of elevated intracellular levels or whether the circulating ADMA itself is physiologically active. There is worry that the normal concentrations found in healthy individuals (500 nmol/L to 1.2 μmol/L) or numerous illness conditions (up to ≈ 3 μmol/L) are too low to have any biological effect.

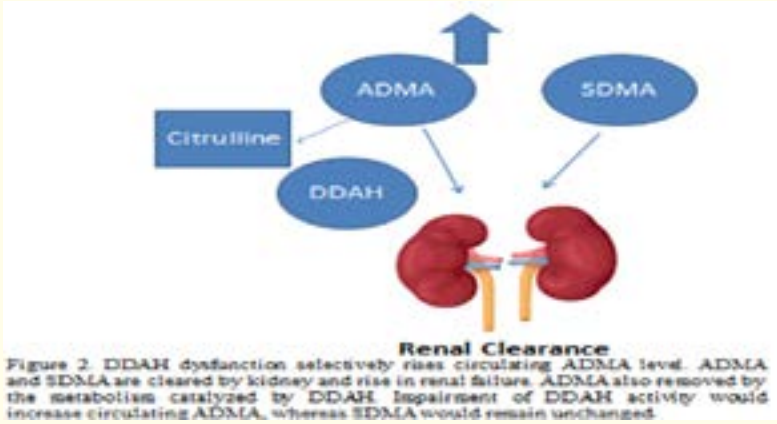

Figure 2. DDAH dysfunction selectively rises circulating ADMA level. ADMA and SDMA are cleared by kidney and rise in renal failure. ADMA also removed by the metabolism catalyzed by DDAH. Impairment of DDAH activity would increase circulating ADMA, whereas SDMA would remain unchanged.

Figure 2: *DDAH dysfunction selectively rises circulating ADMA level. ADMA and SDMA are cleared by kidney and rise in renal failure. ADMA also removed by the metabolism catalyzed by DDAH. Impairment of DDAH activity would increases circulating ADMA, whereas SDMA would remain unchanged.*

The relative concentrations of ADMA and arginine are the cause for concern with regard to ADMA. The quantities of arginine within cells can range from 1 to 2 mmol/L, while plasma concentrations are in the range of 30 to 100 μmol/L [40]. Given the enormous amount of arginine present, ADMA ought to be inert and not be expected to inhibit NOS. Despite the theoretical worries, experimental data suggests that even at very low concentrations, methylarginines have significant impacts. Infusions of ADMA into healthy volunteers reveal that when plasma concentrations of ADMA are within the pathophysiological range, there are increases in blood pressure and vascular resistance as well as a decrease in cardiac output and heart rate [41,42]. It's interesting to note that the heart rate dropped significantly and quickly even before improvements in vascular resistance became apparent. This shows that rather than reflex effects secondary to hemodynamic effects, the effects on heart rate may be a direct influence on NOS systems in the heart.

There appears to be a difference between species in the percentage of circulating ADMA removed by renal excretion and by DDAH activity. According to estimates, the bulk of ADMA in rats (about 90%) is digested, with only a little portion showing up unchanged in urine [43-45]. Infusions of ADMA stimulate the synthesis of dimethylamine in humans, indicating significant DDAH activity [46]. In fact, it has been determined that each day, 260 μmol (or 50 mg) of ADMA are metabolised, and 60 μmol are excreted. When it comes to renal tubular NOS activity, the amount in urine is sufficient to produce concentrations as high as 20 to 30 μmol/L. Plasma ADMA concentrations should raise by as much as 5 μmol/L per day if ADMA removal is completely unsuccessful. This finding has the conclusion that considerable short-term variations in plasma ADMA levels are improbable. In fact, unless there is considerable proteolysis causing a quick rise in ADMA release or a sudden transit of ADMA from tissue into plasma, some of the rapid changes found in some studies are difficult to comprehend.

Asymmetric dimethyl arginine in critical illness

Critical illness has been linked to elevated ADMA levels and, consequently, the arginine-nitric oxide pathway [45]. It has been demonstrated that serum levels of ADMA, which build in critically sick patients, are exposed to increased levels [46]. Hepatic and renal failures, two organs that are vital in critical disease, are the main causes of elevated ADMA plasma levels [47]. High amounts of ADMA were detected in critically ill patients with hepatic failure. Higher systemic levels of ADMA were the result of the removal of liver tissue and prolonged hepatic damage, which affected the liver's ability to eliminate ADMA. Additionally, it appears that hepatic failure is linked to high levels of ADMA [48]. Furthermore, diminished renal function was associated with lower renal clearance in wild-type mice with leftover kidney disease [49]. Additionally, almost all ICU patients experience insulin resistance, which leads to hyperglycemia and impairs DDAH function [50]. Accordingly, it was discovered in an animal model that intense insulin therapy reduces the plasma concentrations of ADMA in critically ill patients and may increase the functioning of DDAH [51]. According to Ellger., *et al*. explanation's rather than having an impact on the release of dimethylarginine due to protein catabolism, ADMA breakdown may have been protected by preserving physiological DDAH activity [52]. Critically ill patients have high amounts of ADMA when combined. This is supposedly caused by the patient being in a catabolic condition, which causes a fast turnover of proteins containing dimethylarginine and renal and hepatic failure, which alters DDAH function and causes reduced excretion.

Human ICU morbidity and death are increased by elevated ADMA levels [53]. The significance of the arginine: ADMA ratio must be recognised in order to comprehend the negative consequences of ADMA and the necessity of nitric oxide for survival in critical illness. This route has been thoroughly investigated in both human and animal sepsis and organ dysfunction conditions [54-57]. Vascular and organ dysfunction that is brought on by endothelial damage and microvascular oxidative stress characterises critical illness [58]. Nitric oxide regulation of organ perfusion in this condition is crucial because organ oxygenation is at danger. In the severely ill state, high levels of ADMA reduce the arginine: ADMA ratio, obstruct NOS and CAT, and subsequently reduce the synthesis of nitric oxide. Therefore, it is conceivable that the pathological processes of critical disease may be influenced by the elevated ADMA levels.

A rat study was conducted to better understand the relationship between nitric oxide and the arginine: ADMA ratio in sepsis. The impact of nitric oxide production suppression upon endotoxemia was examined in an isolated perfused rat heart. The endotoxin-treated rats experienced severe coronary vasodilation, which was brought on by an enhanced nitric oxide release. After endotoxemia, inhibition of nitric oxide metabolism resulted in decreased coronary flow and regions of myocardial ischemia. After receiving arginine as a nitric oxide substrate, these spots vanished. In a different model of critically ill rats, systemic hemodynamic (heart rate, mean arterial pressure, and cardiac output) deteriorated and blood flow through the kidney, spleen, and liver was decreased when low arginine plasma levels were combined with high ADMA plasma levels (low arginine: ADMA ratio). When volunteers receiving an intravenous low-dose of ADMA displayed lower heart rate, cardiac output, and higher mean blood pressure when compared with controls, studies in humans supported these findings [59]. Nitric oxide production in septic patients may be abnormally high, which can be dangerous [60]. Therefore, it was suggested that inhibiting NOS might be a way to lower morbidity and death in this patient population. In order to prevent the overproduction of nitric oxide, one trial evaluated the impact of a NOS inhibitor in a population of 124 septic patients [61]. Because of the 28-day death rates of 59% in the NOS inhibitor group and 49% in the placebo group, the experiment was temporarily terminated. The majority of the study participants who passed away before completion had cardiac causes of death. Overall, numerous investigations have demonstrated that ADMA at high concentrations can have negative effects. These negative effects are mostly brought about by decreased nitric oxide availability, which causes altered vasodilatation and antithrombotic, anti-inflammatory, and antiapoptotic effects that collectively may cause cardiac dysfunction [62].

ADMA is a novel cardiovascular risk factor

Research were shown that circulating ADMA levels are elevated in patients with systemic atherosclerosis, in clinically healthy human subjects with isolated hypercholesterolaemia, in patients with essential hypertension, and in patients with renal failure. These findings

follow the initial characterization of ADMA as endogenous inhibitor of NO synthase by Vallance., *et al* [63]. The number of clinical conditions with increased ADMA levels has continued to increase (Table 1). The most recent studies point to a pathophysiological role for ADMA in restricting NO availability in pulmonary hypertension and sickle cell disease. The first study to establish higher ADMA levels in individuals with congenital heart disease and pulmonary hypertension was conducted by Gorenflo., *et al*. in this field. By demonstrating that DDAH activity is dysregulated in chronic hypoxia-induced pulmonary hypertension and that ADMA levels are higher and ADMA catabolism is lower in individuals with idiopathic pulmonary hypertension, these findings were furthered. According to Kielstein., *et al*. [64] research, increased ADMA levels in patients with idiopathic pulmonary hypertension may have predictive significance.

Condition	x-fold increase
Chronic renal failure	2 to 7-fold
Pregnancy-related hypertension	2-fold
Chronic heart failure	2 to 3-fold
Pulmonary hypertension	2 to 3-fold
Diabetes mellitus II	2 to 3-fold
Liver failure	2-fold
Hyperhomocysteinemia	2-fold
Hypertension	2-fold
Insulin resistance	2-fold

Table 1: *Pathophysiological conditions in which ADMA was reported to be increased. The x-fold increase in patients with the clinical condition indicated as compared to healthy subjects.*

A pathophysiological role for ADMA in the aetiology of vascular dysfunction and cardiovascular disease in humans has also been demonstrated by a number of prospective studies that used surrogate endpoints for cardiovascular disease. In a study involving 116 clinically healthy human participants, high ADMA levels were discovered to be related to carotid artery intima-media thickness. Another study conducted in haemodialysis patients found that ADMA predicts the progression of intimal thickening throughout one year of follow-up, taking this result further in a prospective design. High ADMA levels were linked to a 3.9-fold increased risk for acute coronary events in a nested, case-control study involving 150 middle-aged, non-smoking men [65].

In 2001, after three years of follow-up, we reported the first prospective clinical trial on ADMA as a predictor of cardiovascular outcome and total mortality in 225 patients receiving haemodialysis [66]. Patients in this study had a three-fold increased chance of dying from any cause than those whose ADMA levels were below the median or within the top quartile at the start of the study.

Another study looked into variables that affected how patients treated in intensive care units for various conditions fared. When compared to patients with ADMA levels in the lowest quartile, patients with ADMA levels in the highest quartile had a 17-fold higher rate of mortality. The outcome of patients with stable angina pectoris following coronary balloon angioplasty was examined in a third prospective study [67]. Inclusion criteria for the study were 153 stable angina pectoris patients who received elective coronary angioplasty. Patients were tracked for a median of 16 months after being divided into tertiles of pre-procedural ADMA. Throughout the follow-up, 51 significant cardiovascular events took place. Interestingly, the risk of a cardiovascular event rose with ADMA levels and was independent of other risk factors in a multifactorial Cox's regression analysis (including age, smoking, hypercholesterolemia, stent use, and others).

By demonstrating that ADMA is higher in patients with acute coronary syndrome than in individuals with stable angina pectoris, we have recently expanded on the information already accessible. Patients with unstable coronary syndrome who saw their ADMA drop to

levels comparable to those of those with stable coronary artery disease within six weeks of the acute episode in a prospective follow-up had fewer major cardiovascular events over the course of a year of monitoring than those who's ADMA had remained elevated [68].

An examination of 1,874 participants from the AtheroGene study group found a highly significant and independent link between raised ADMA concentration and an increased risk of major cardiovascular events over a mean follow-up of 2.6 years.

Data on ADMA as a cardiovascular risk factor from prospective clinical studies are summarised in figure 2. Other cardiovascular risk factors and confounding factors were taken into account in the analysis of each of these trials, and ADMA was discovered to be an independent predictor of cardiovascular events. Consequently, it has recently been determined that ADMA can be thought of as a unique cardiovascular risk factor [69].

Conclusion

It is concluded that ADMA is an important measure in patients receiving intensive care. Additionally, it undergoes production, metabolism, and excretion. This paper describes in detail how ADMA increases in critically ill patients with sepsis as well as cardiovascular patients.

Author's Contribution

Mohd Rafi Reshi created the concept and designed the structural of the manuscript and involved in the preparation of the manuscript. Muzammil Muzaffar, Afshana Bashir Reshi and Aabida Majid also added some part in this article. Saman Anees and Maaz Naqvi, also making some changes and adding some study material. Mohd Rafi Reshi and Maaz Naqvi make all over review, design and abstract of manuscript.

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