

Effect of Certain Pharmacotherapies on Plasma Asymmetric Dimethyl Arginine (ADMA)

Patil T R^{1*}, Patil S², Patil A³, Patil S T⁴

¹Department of Pharmacology, Bharati Medical College and Hospital, Sangli, Maharashtra, India

²Department of Public Health Dentistry, School of Dental Sciences, Karad, Maharashtra, India

³MDS, Oral pathologist

⁴MBBS, DGO, Gynecologist

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ABSTRACT

Asymmetric dimethyl arginine [ADMA] is a nitric oxide synthase inhibitor and reduces nitric oxide [NO] generation. It is considered an important cardiovascular risk marker. It is raised in various clinical conditions like hypertension, ischemic heart disease, cardiac failure, diabetes mellitus, obesity and toxemia of pregnancy. Certain drugs used to treat these conditions have additional ADMA lowering property which reflects in to good cardiac outcome. These drugs are angiotensin converting enzyme inhibitors, angiotensin receptor blockers NO generating beta blockers, antidiabetic drugs like metformin and pioglitazone and hydrophilic statins which are used to treat these conditions. Low dose aspirin and estrogen, L-arginine, various antioxidants and homocysteine lowering drugs are associated with fall in ADMA levels. Hence awareness about the ADMA lowering potential of these drugs offers an additional benefit than their peers leading to better cardiac prognosis. Drugs like proton pump inhibitors; antiepileptics like carbamazepine and sodium valproate and also COX 2 inhibitors are observed to raise ADMA levels. Hence their choice should be done carefully and cautiously.

Keywords: Asymmetric dimethyl arginine, nitric oxide synthase, nitric oxide, cardiovascular outcome

INTRODUCTION

Endothelium derived mediators like nitric oxide [NO] and prostacycline are potent vasodilators and they play an important role in vascular homeostasis. NO is formed by endothelial isoform of nitric oxide synthase [NOS] i.e eNOS. NO induces vasodilatation¹, inhibits aggregation of platelets², suppresses vascular smooth muscle cell proliferation³ prevents oxidation of LDL⁴. It inhibits leucocyte and monocyte adhesion to the endothelium⁵. It also suppresses the expression and activity of adhesion molecules and chemokines which are known to initiate vascular inflammation⁶. NO is an important endogenous anti atherosclerotic molecule. Decrease in NO due to endothelial dysfunction enhances atherosclerosis and cardiovascular risk^{7,8}.

Naturally occurring endogenous inhibitor of NOS is an asymmetric dimethylarginine [ADMA]. This reduces NO production and initiates endothelial dysfunction⁹. Plasma ADMA is a putative cardiovascular risk marker. Degradation of methylated proteins results in to formation of dimethylarginines¹⁰. The methyl groups are derived from S adenosylmethionine. Enzymes protein arginine methyl transferases type 1 and 2 [PRMT 1 and PRMT 2] are involved in this reaction. PRMT1 catalyses the formation of NG NG dimethyl L arginine [ADMA] and NG monomethyl L arginine [L-NMMA]. PRMT 2 participates in the generation of symmetric dimethyl arginine[SDMA]. ADMA and L- NMMA and not the SDMA are the competitive inhibitors of NOS¹¹⁻¹³.

Elevated plasma ADMA enhances all cause cardiovascular mortality¹⁴⁻¹⁶. Endothelial release of ADMA is also triggered by LDL and oxidized LDL [ox LDL] probably by upregulating s-adenosylmethionine dependent methyl transferase¹¹.

ADMA gets metabolized via its hydrolytic degradation to citrulline and dimethylamine. Enzyme NG dimethylarginine dimethylaminohydrolase [DDAH] catalyses this reaction¹⁷. DDAH -1 and DDAH-2 are the two isoforms of DDAH. DDAH 2 is formed predominantly in tissues containing endothelial isoforms of eNOS and DDAH -1 in tissues expressing neuronal NOS [iNOS]¹⁸. But Xinli Hu et al. [2011] by using endothelial specific DDAH 1 deficient mouse found that endothelial DDAH 1 is important for degrading ADMA and maintaining NO bioavailability¹⁹. Increased ADMA, inhibition of eNOS and DDAH have been correlated with negative prognosis associated with cardiovascular diseases and other conditions. In various studies ADMA was found to be raised in hypertension²⁰⁻²³, coronary artery disease^{15,24,25}, congestive heart failure²⁶⁻²⁸, atherosclerosis^{29,30}, stroke^{6-8,31,32}, hypertrophic cardiomyopathy³³, peripheral arterial diseases^{34,35}, pulmonary hypertension³⁶, diabetes mellitus³⁷⁻³⁹, hyperlipidemia^{11,40}, hyperhomocysteinemia^{31,41}, obesity⁴², liver cirrhosis^{43,44}, renal failure^{9,38,45-47} toxemia of pregnancy^{48,49} and Alzheimer's disease⁵⁰. Hence it becomes imperative to study the drugs which modify the plasma levels of ADMA which could be considered as follows.

Drugs which decrease the levels of ADMA- Hypolipidemic agents –

Statins are promising drugs in reducing cardiovascular risk by correcting hyperlipidemia and due to their pleiotropic effects beyond lipid lowering which improve endothelial function and increase bioavailability of NO^{40,51}.

Clinical studies have correlated high LDL cholesterol levels with elevated plasma ADMA concentration^{40,51}. Hence it was expected that by decreasing LDL levels statins should also bring down raised ADMA levels. This hypothesis was tested by many investigators⁵²⁻⁵⁴. Studies have shown that rosuvastatin could bring down ADMA levels. It also reduced the levels of 8- isoprostanes, the markers of oxidative stress⁵⁵.

In experimental studies atorvastatin was administered in rats with arterial hypertension for prolonged period and was found to bring down the levels of ADMA⁵⁶. Patients with metabolic syndrome and hyperlipidemia, when received fluvastatin in dose of 80 mg/day for period of 6 weeks were found to have reduced levels of ADMA⁵⁷. Systematic meta analysis was done by Corina Serban et al [2015] to study the effects of various statins on serum ADMA levels. They found that serum ADMA levels were decreased significantly by hydrophilic statins like rosuvastatin, pravastatin and fluvastatin and not by hydrophobic statins like simvastatin and atorvastatin⁵⁸.

Fenofibrate another hypolipidemic agent which mainly brings down triglyceride levels was found to reduce ADMA and TNF α levels. It also inhibited lipid peroxidation in hyperlipidemic rats and improved endothelial function⁵⁹. Fenofibrate also prevented activation of nuclear factor kappa B resulting in to activation of PPAR α receptors⁶⁰.

Ezetimibe an inhibitor of cholesterol absorption from GI tract could bring down ADMA levels in diabetic dyslipidemics with renal injury in cholesterol independent manner⁶¹. Ezetimibe was found to influence ADMA/DDAH/NO pathway favorably in rat model⁶².

Another hypolipidemic agent probucol has additional antioxidant property. It was found to reduce elevated ADMA levels and inhibit lipid peroxidation and LDL in experimental conditions^{63,64}. It decreased ADMA levels along with reduction in PRMT 1 expression and increase in DDAH activity resulting into increased expression of eNOS⁶⁵.

Beta blockers

Beta-blockers have been proved to be cardioprotective due to their various underlying mechanisms. ADMA is a proved risk factor for cardiovascular diseases, atherosclerosis and acute coronary events. But except NO generating beta blockers like nebivolol other beta blockers like besoprolol, atenolol and metoprolol did not reduce elevated ADMA concentrations⁶⁶⁻⁶⁸.

Nebivolol was found to decrease ADMA/ SDMA ratio and increase DDAH – 2. m RNA and protein expression in dose dependent manner⁶⁹. With nebivolol, expression of eNOS and DDAH2 were upregulated and PRMT 1 expression was downregulated⁷⁰. Nebivolol ameliorated ADMA induced vascular response in rat aorta which was

partly attributed to the mechanism involving beta 3 adrenoreceptors⁷¹.

Carvedilol is another beta blocker which was found to decrease ADMA levels in patients of heart failure and also reduced the inflammatory mediators like interleukin-10⁷². Esmolol was found to reduce ADMA activity and enhance DDAH activity resulting into protective effect on left anterior descending coronary artery remodeling⁷³.

Antidiabetic drugs

Diabetes mellitus increases the mortality due to its cardiovascular complications and accelerated atherosclerosis. Endothelial dysfunction resulting into decreased NO generation reflects into impaired NO dependent vasorelaxation⁷⁴.

NO deficiency arises due to increased concentration of ADMA in uncontrolled diabetes mellitus⁷⁵. Increase in ADMA level also correlates with high oxidative stress in diabetes with increased lipid peroxidation and excessive generation of free oxygen radicals which inactivate DDAH possibly by activation of xanthine oxidase and inactivation of superoxide dismutase (SOD)⁷⁶.

ADMA levels were found to be reduced with correction of hyperglycemia⁷⁷. Antidiabetic drug metformin reduced ADMA levels which was unrelated to control of hyperglycemia in women with polycystic ovarian syndrome (PCOS)^{78,79}. Raised ADMA levels in these patients correlated well with parameters of insulin sensitivity⁷⁸. Metformin is a structural analogue of ADMA. In experimental studies done by Tsai C M et al, they found the restoration of raised ADMA levels in hypertensive rats and also a fall in B. P.⁸⁰ Metformin did not modify the levels of DDAH1 and 2 and NO synthase activity but raised NO levels in kidney⁸⁰.

Pioglitazone which is PPAR gamma agonist was found to decrease ADMA levels by enhancing DDAH activity in experimental conditions⁸¹. Study was done by Tahara N et al in diabetic patients and also in patients with impaired glucose tolerance who received pioglitazone. They found a reduction in ADMA levels in glucose lowering independent manner. Rise in fibronectin by pioglitazone was thought to contribute for ADMA lowering effect⁸².

Similarly, rosiglitazone, another thiozolidinedione improved insulin sensitivity and also reduced ADMA levels in patients of insulin resistance and hypertension⁸³. PPAR/ PXR binding sites have been found in the promoter region of DDAH 2 which could explain the effect of PPAR gamma agonist on ADMA and DDAH⁸⁴.

Angiotensin converting enzyme inhibitors[ACEI] and angiotensin receptor blockers[ARBs] –

Hypertension, diabetes mellitus and coronary artery disease are invariably associated with endothelial dysfunction and decreased NO availability. ACEI and ARBs were found to improve endothelial function with increased NO availability⁸⁵⁻⁸⁷. This was due to impaired bradykinin degradation and increased NO release as a result of blockade of angiotensin II effect on AT 2 receptors^{88,89}. Angiotensin II by activating NADPH oxidase increases the production of superoxide anions⁹⁰ and raises ADMA levels^{91,92}. Administration of ACEI and ARBs in hypertensive patients was correlated with

significant drop in plasma ADMA levels^{66,91-93} ACEI like captopril⁹⁴ and zofenopril⁹³ which possess SH group, were found to have antioxidant effect with reduction in ADMA levels and improved endothelial function. Experimental studies have shown that ADMA increased oxidative stress which could be NO independent effect, through upregulation of ACE and through AT 1 dependent pathway. This was found to be inhibited by ACE- I and ARBs⁹⁵. Hideki Fujii et al studied the effects of both ACEI and ARBS in normotensive patients with chronic kidney disease. They observed reduced levels of ADMA and oxidative stress in them⁹⁶.

ARB like telmisartan which is a metabolic sartan has got property to activate PPAR gamma signaling

Ageing endothelium leading to endothelial dysfunction was found to have decreased PPAR gamma protein expression and increased expression of AT1 receptor. Telmisartan reversed this process. Additionally, it increased activity and protein expression of DDAH and decreased ADMA concentration. This effect of telmisartan was prevented by blocking PPAR gamma signaling⁹⁷. Decreased ADMA levels with telmisartan could be associated with decreased expression of PRMT 1 as was suggested by experimental studies done in diabetic rats⁹⁸.

Hormone replacement therapy-estrogens

Hormone replacement therapy was observed to improve endothelial function and NO generation^{99,100}. Increased DDAH activity and subsequent fall in ADMA was the suggested mechanism for increased NO generation after studying the effect of estradiol on endothelial cell cultures^{101,102}. Structure of estradiol is similar to tocopherol¹⁰³ and it also has antioxidant property. It protects the endothelium, enhances NO synthesis, inhibits leucocyte adhesion, aggregation of platelets and prevents proliferation of vascular smooth muscle cells¹⁰⁴⁻¹⁰⁷. Estradiol also reduces LDL oxidation^{108,109}. Clinical studies conducted in 40 females with estrogen hormonal replacement therapy showed significant drop in ADMA levels¹⁰⁸. Holden D.P. [2003] found rise in enzyme DDAH and fall in ADMA levels in postmenopausal women who were put on estrogen replacement therapy and also in human cell culture lines¹⁰¹.

Aspirin-

Low dose aspirin is an antiplatelet agent and it protects the endothelium against LDL induced oxidative damage. This protective effect is attributed to increased concentration of DDAH resulting into reduction in ADMA levels¹¹⁰. ADMA is known to accelerate cellular senescence¹¹¹. Aspirin delays senescence, decreases reactive oxygen species, increases nitric oxide and c GMP levels. Upregulation of DDAH by aspirin resulted in to decreased ADMA activity¹¹². Aspirin was also found to reduce hypercholesterolemia induced increased TNF alpha which is known to inhibit DDAH and elevate ADMA levels^{110,113}.

Agonist of farnesoid X receptors-

Farnesoid X receptors regulate the metabolism of lipids and carbohydrates and their intermediate products^{114,115}. These receptors may modulate ADMA levels by regulating DDAH 1 and also CAT 1 activity. Farnesoid receptor agonist like GW 4064 under experimental conditions

increased the expression of genes for DDAM 1 and CAT 1^{116,117}.

Antioxidants-

Antioxidants by reducing oxidative stress restore DDAH activity and result in to decrease in ADMA levels^{76,118,119}. Well known strong antioxidant Vit. E inhibits lipid peroxidation, reduces hypercholesterolemia and improves endothelium dependent vasorelaxation by reducing ADMA levels^{120,121}.

Folic acid, Vit. B6, Vit. B12, Vit. A-

Study done by Holven K B et al showed reduced homocysteine and ADMA levels with folic acid^{122,123}. But Vit B6 which is a cofactor for transformation of homocysteine to cystathionine and of Vit B 12 in to methionine did not show effect on ADMA levels¹²⁴. Vit A derivatives, in particular all trans-retinoic acid have been shown to increase DDAH- 2 expression and activity and enhanced the decomposition. of ADMA. This effect is related to regulation of enzyme gene transcription⁸⁴.

L-arginine-

L-arginine is a main substrate for NO synthase, deficiency of which results in to decreased NO synthesis¹²⁵. Deficiency of arginine or of tetrahydrobiopterin[BH4] a cofactor of eNOS results in to uncoupling of eNOS which generate peroxynitrite under oxidative stress¹²⁶. In patients with hyperlipidemia L- arginine therapy reduced elevated ADMA levels and improved endothelium dependent vasorelaxation⁴⁰. Supplementation of L-arginine in therapeutic doses seems to be the most effective and promising way to reverse the detrimental effect of ADMA on endothelial cells.

Aminoguanidine-

It is a selective iNOS inhibitor and also possess antioxidant activity¹²⁷. This prevents formation of advanced glycosylation end products[AGEs]in diabetes mellitus¹²⁸. These products increase oxidative stress and vascular damage in diabetics¹²⁸. Aminoguanidine was found to reduce ADMA levels and increase the activity of NOS, DDAM and SOD¹²⁹.

Demethylbellidifolin

Demethylbellidifolin is the main compound of Chinese herb Swertia davidi. It inhibits lipid peroxidation, LDL oxidation, and reduces ADMA levels and thus protects endothelium^{130,131}.

Green tea-

Epigallocatechin is the main compound in green tea responsible for antioxidant effect¹³². Experimental studies done with this compound showed reduction in ADMA activity and improvement in DDAH activity probably by inhibiting proinflammatory cytokines like TNF alpha^{113,132}. It also enhanced eNOS activation¹³³.

N-acetylcysteine-

N-acetylcysteine contains thiol molecule and possesses antioxidant property. It was found to decrease reactive oxidant species and increase in DDAH activity resulting in to reduced ADMA levels in patients of end stage renal disease¹³⁴. When N-acetyl cysteine was administered in 48patients who were on hemodialysis, they were found to have lowered plasma ADMA levels¹³⁵.

Drugs which elevate the levels of ADMA adversely-

Antiepileptic drugs-

Serum homocysteine and ADMA levels were elevated in epileptic children receiving valproic acid for about 2 years in higher dosages. ADMA is considered as a better indicator of endothelial dysfunction as compared to homocysteine as it is less sensitive to changes such as fasting states, physical activity and other factors¹³⁶. Similarly, Oz O found significant rise in levels of ADMA in epileptic patient treated with either valproic acid or carbamazepine which were the factors for increased cardiovascular risk in them¹³⁷.

Proton pump inhibitors-PPI

Recent in vivo data suggests that PPI increased ADMA levels due to inhibition of enzyme DDAH which explains the increased cardiovascular risk in patients with indiscriminate use of PPI. In experimental studies with cultured human cells and in mice PPI were found to increase intracellular ADMA levels causing endothelial dysfunction. Thus PPI by inhibiting DDAH enhance ADMA levels and inhibit eNOS. This results into reduced generation of NO leading to enhanced atherosclerosis affecting cardiovascular mortality adversely¹³⁸.

Nonsteroidal anti-inflammatory drugs-NSAIDs

NSAIDs inhibit the enzyme cyclooxygenase [COX] and prevent the generation of inflammatory prostaglandins and also that of thromboxane [TXA₂] and prostacycline, [PGI₂]. TXA₂ is proaggregatory and PGI₂ is antiaggregatory for platelets and thereby they either induce thrombosis or prevent it. NSAIDs are either nonselective inhibitors of COX 1 and COX2 or selective inhibitors of COX2. Recent rise in cardiovascular mortality due to COX 2 inhibitors like rofecoxib is a major cause of concern. This was attributed to increased thrombosis and atherosclerosis due to loss of vasculoprotective PGI₂. Inhibition of renal medullary COX2 causes water and sodium retention and induces rise in blood pressure. Study done by Blerina Ahmetaj shala et al [2015] identified the rise in endothelial nitric oxide synthesis inhibitor ADMA, as a biomarker a link between renal COX2 inhibition and systemic vascular dysfunction leading to increased cardiac mortality. They also conducted human studies with selective COX2 inhibitor like celecoxib and nonselective COX inhibitor like naproxen. Both drugs were found to inhibit COX 2 by about 80% at therapeutic dosages. They also increased ADMA levels¹³⁹.

Framingham study done in large population showed that even a relatively small rise in ADMA levels are associated with significant rise in cardiovascular events¹⁴⁰. ADMA and L-NMMA are correlated with cardiovascular risk in various clinical studies^{29,36,141-143}. This is very relevant and important as COX 2 selective inhibitor drugs like celecoxib and rofecoxib increase cardiovascular risk even in healthy subjects.

Thus COX2/eNOS axis involving ADMA is very important in explaining NSAID induced increased cardiac mortality. As inhibition of eNOS is the culprit, it suggests the use of L-arginine as a preventive measure in all high risk patients taking NSAIDs¹⁴⁴.

Genetic mutations in genes like PRMT 1 and DDAH 1 need to be screened as they are associated with high cardiovascular risk in NSAID consuming patients.

CONCLUSION

Many studies have been conducted to confirm the effects of various drugs on serum ADMA levels. Raised ADMA levels by inhibiting eNOS and by eventual decline in NO generation herald negative cardiovascular prognosis. Many clinical conditions are associated with raised ADMA levels. Potential of various drugs to reduce raised ADMA levels can be used to treat these conditions. This can definitely offer good clinical outcome. Choice of angiotensin converting enzyme inhibitors and angiotensin receptor blockers for hypertension, cardiac failure and diabetic nephropathy was found to be associated with fall in ADMA levels. ADMA was also found to be reduced by other drugs like NO generating betablockers, antidiabetics like metformin and pioglitazone and hydrophilic statins. Therapy with low dose oestrogen, low dose aspirin, L-arginine and antioxidants was observed to have decline in ADMA levels. Thus the choice of drugs which have potential to reduce ADMA levels for various clinical conditions results in to better cardiac outcome. One need to keep in mind that drugs like proton pump inhibitors, antiepileptics like carbamazepine and sodium valproate and also COX 2 inhibitors can increase serum ADMA levels. Hence their use warrants a caution.

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