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Fluctuation of Asymmetrical Dimethylarginine (ADMA) and Symmetrical Dimethylarginine (SDMA) Levels in Diabetes Mellitus and Obesity

Damiati SA and Khoja SM*

Department of Biochemistry, King Abdulaziz University, Saudi Arabia

***Corresponding author:** Samir Khoja, Department of Biochemistry, King Abdulaziz University, Saudi Arabia, E-mail: skhoja@kau.edu.sa

Mini Review

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Introduction

L-Arginine is a semi-essential amino acid in human that is considered as one of the most metabolically versatile amino acids [1]. It serves as a precursor for the synthesis of nitric oxide (NO) and urea, and participates in the synthesis of creatine, proline, agmatine, glutamate, anabolic hormone simulation and nitrogen balance improvement [1,2]. Indeed, L-Arginine is a free radical scavenger and protective agent against endothelial damages and some chronic diseases [3,4]. However, NO molecules have multiple functions in the physiology and pathophysiology of the immune, nerve, and cardiovascular systems including vasodilatory, anti-thrombotic and anti-atherogenic effects in the vasculature [5]. It has been reported that L-Arginine supplementation increases some antioxidant enzyme activities in patients with ischemic heart disease [6].

Three L-Arginine methylated derivatives are released during protein turnover: N^G-monomethyl -L- arginine (L-NMMA), asymmetrical dimethylarginine (ADMA) and symmetrical dimethylarginine (SDMA) (Figure 1). These derivatives are generated when L-Arginine incorporated into peptide linkage in proteins and demythelated after being released when the proteins are catabolized [7]. Production of these derivatives requires several enzymes; N-methyl-transferase to convert arginine to NMMA, which methylated by N-methyl-transferase I and II to form ADMA and SDMA, respectively [8]. The three methylarginines are able to decrease NO production. Free NMMA and ADMA act as inhibitors for nitic oxide synthase (NOS) with different potencies for different isoforms. Both are competitive inhibitors for arginine transport while SDMA inhibits the transport of arginine only [8-10].

Methylarginines are eliminated from the body by urinary excretion. In rabbits, SDMA has been shown to be 30 times higher than that of L-NMMA and ADMA [11]. Hence, several studies have linked increased concentrations of intercellular level of ADMA and SDMA with renal failure [12-15]. However, by the alternative non-renal route, L-NMMA and ADMA, but not SDMA, it can be metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) to L-citrulline and dimethylamine [16-18]. The active form of DDAH found in liver, kidney, brain, pancreas with immune expression in neutrophils and macrophages [19,20]. There are two forms of DDAH: DDAH-1, which are found in tissue expressing neuronal NOS and DDAH-2, which are found in tissue containing the endothelial isoform of NOS [16,21]. Elevated levels of glucose, oxidized LDL-cholesterol, homocysteine, and oxidative stress are associated with decreased levels of DDAH and reduced production of NO [22-24].

The circulating levels of endogenous L-NMMA are lower than ADMA and SDMA. Later, the two are present in concentration range of 500nM to 1μM in healthy humans [25]. Both are able to reduce NO production indirectly by inhibiting the cellular uptake of the NO precursor L-Arginine [24]. Therefore, elevated levels of plasma ADMA and SDMA can be linked to atherosclerosis and renal failure [12-17,25-27]. This review is focusing on ADMA and SDMA as risk markers that are associated with

endothelial vasodilator dysfunction in diabetes mellitus and obesity, which are both major growing health issues worldwide.

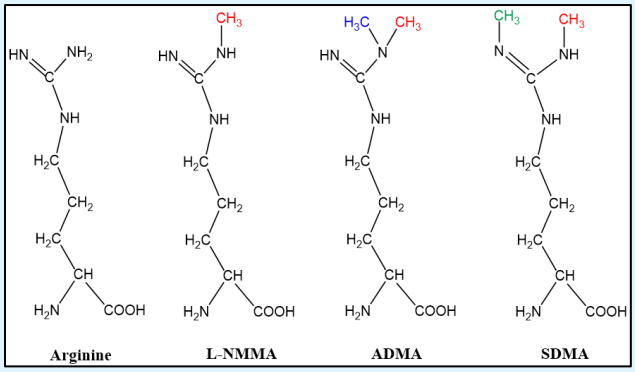

Figure 1: Structure of Arginine, N^G-monomethyl-L-arginine (L-NMMA), Asymmetrical dimethylarginine (ADMA) and symmetrical dimethylarginine (SDMA).

ADMA, SDMA and Diabetes Mellitus

Hyperglycemia defines the diabetic state which is common to type 1 and 2 diabetes. Glucose plays a significant role in atherogenesis and might damage arterial cells [28]. However, impaired NO mediated vascular response is associated with the development of atherosclerosis and different diabetic vascular complications in diabetes [27,29]. Indeed, NO has a direct influence on insulin sensitivity. For example, gene disruption of NOS exhibited insulin resistance in the vasculature in mice [30].

Deficiency of Arginine and reacting of reactive oxygen species (ROS) with NO leads to reduction in the NO availability [31-33]. This reduction with increased oxidative stress is involved in increased renal cortical cellular oxygen consumption in long-term hyperglycemia [33-35]. Moreover, it is well known that diabetes is associated with an elevated risk of clinical cardiovascular disease (CVD) and with accelerated atherosclerosis, which has become the main cause of morbidity and mortality in patients with diabetic nephropathy [36]. Therefore, several strategies have been reported based on arginine to improve insulin secretion and pancreatic beta-cell protection in diabetes [37,38].

Several studies have investigated the circulating levels of ADMA and SDMA in diabetes. In most metabolic disorders, ADMA shows higher levels than normal, which is identified as a predictor of cardiovascular event, but in type 1 and 2 diabetes ADMA level is less consistent. It appears that the correlation between ADMA and diabetes mellitus is fluctuated and causesa lot of controversy. Several studies showed that ADMA concentrations differed significantly between diabetic children and the healthy sex-matched controls as type 1 diabetic group had higher concentration of ADMA [29,39-41]. Indeed, it has shown a close correlation between ADMA levels and indices of insulin sensitivity resistance. This can be explained due to the high level of glucose, which suppresses DDAH activity and leads to increased ADMA concentrations in blood and urine [8]. The association between ADMA and type1 diabetes has been examined by Tarnow et al., in 2004. They found that patients with type 1 diabetes and early nephropathy have higher concentrations of ADMA while the correlation between ADMA and glomerular filtration rate (GFR) was negative [29]. In contrast, other studies showed that ADMA level is lower, or similar in children and adolescents with type 1 diabetes compared with healthy subjects [42-44]. It has been assumed that ADMA may protect the system from the overproduction of NO and perpetuation of oxidative stress [43]. However, this conflict in ADMA levels can be explained by changes in DDAH activity. This enzyme is influenced significantly by diabetes and diabetes therapy [45,46]. Differences in ADMA levels in diabetic patients are associated with the variations in DDAH-1 and DDAH-2 genes, and with insulin sensitivity in non-diabetic subjects [47].

Similar to type1 diabetes, the distribution of ADMA levels is differed among hyperglycemic patients with type 2 diabetes. In some clinical investigations, there was a direct correlation between elevated levels of ADMA and glucose in type2 diabetes and that contributes to the accelerated coronary heart disease, which is the major cause of mortality and morbidity in these patients [48-51]. It has been reported that strict glycemic control possibly exerts anti-atherogenic effects by lowering ADMA concentration in type 2 diabetic patients [52].

In parallel to ADMA, SDMA is also implicated in endothelial dysfunction and long-term cardiovascular risk. It has been reported that elevation of SDMA level is correlated better with the total sequential organ failure assessment score than ADMA in intensive care patients and indicated both hepatic and renal failure [53]. Since SDMA is strictly eliminated by renal excretion, many clinical studies focused on SDMA as a useful parameter for detection of early stage of chronic kidney disease [54,55]. Marcovecchio and his colleagues proved that SDMA is a reliable marker in identifying changes in GFR with the

development of microalbuminuria in children with type1 diabetes [56]. Contrary, Can et al., in 2011 reported that type 2 diabetic patients with poor glycemic control had lower level of SDMA and suggested several mechanisms may lead to this reduction such as hyperfilteration or hypomethylation of arginine residues [57]. Interestingly, Anderssohn et al in 2014, showed that both ADMA and SDMA are weakly related to glycemic state and anti-hyperglycemic medications, and their predictive values for incident CVD in patients with type 2 diabetes are limited [58]. Moreover, the effect of nephropathy on diabetic retinopathy could be mediated by high levels of ADMA and SDMA in type 1 and 2 diabetes, SDAM showed higher level than ADMA especially in patients with nephropathy and severe forms of diabetic retinopathy [29,55,59-61]. Decreased renal clearance of methylarginines possibly lead to elevated plasma levels directly impacting diabetic retinopathy development [62]. Indeed, elevated levels of ADMA and SDAM have been reported in association with advanced glaucoma in type2 diabetes [63].

ADMA, SDMA and Obesity

A variety of peptides such as leptin and adiponectin has important roles in feeding behavior and present a complex interaction among obese individuals. Both leptin and adiponectin are able to modulate the activity of NOS [64-66]. Obesity is associated with methylarginines levels and related to increased protein turnover and to lower insulin sensitivity of protein metabolism. Indeed, it may amplify insulin resistance and endothelial dysfunction. As diabetes mellitus, ADMA and SDMA levels are contradicting in obese subjects [67,68]. Several studies reported elevations of arginine, ADMA and SDMA in obese subjects and strong correlations were found between all three methylarginines and the anthropometric variables (height, weight, BMI, and hip circumferences) are associated with obesity. On the other hand, waist circumference was found as an independent variable predicting plasma concentrations of arginine and SDMA only. Marliss et al., in 2006 found that ADMA is sex and age dependent [67]. Elderly men have higher levels of ADMA than young, lean men and further increased were noticed in obese subjects. This can be explained due to the high level of fat-free mass in obese males and difference in the activity of N-methyltransferase I that affects the rates of protein turnover. In contrast, neither sex nor age have effect on arginine or SDMA levels [67,69]. However, Kocak and his colleagues assessed the plasma levels of ADMA in obese postmenopausal women [64]. They found that these women have higher ADMA concentrations than women with normal body mass index (BMI) due to estrogen deficiency and prone to disturbances in energy homeostasis. Interestingly, elevated levels of ADMA in obese insulin resistant women can be decreased in response to weight loss and thiazolidinedione treatment [70]. Contrary, Cetinalp-Demircan et al in 2007 reported that circulating levels of ADMA remained unchanged while SDMA reduced in premenopausal obese women despite that they have high levels of C-reactive protein (CRP), triacylglycerol, and low levels of HDL-cholesterol, adiponectin, and insulin sensitivity, all of which is closely associated with risk factors for CVD [71].

Conclusion

Available evidence suggests that arginine and its derivatives have an effect on endothelial dysfunctions either directly or indirectly by decreasing NOS activity and NO bioavailability. Diabetes mellitus and obesity increase the risk of many serious health problems and their risk factors might be associated with ADMA and SDMA which possibly mediate deleterious effects by several mechanisms. Hence, it is important to investigate whether ADMA and SDMA are only risk markers, or causative factors for other complicated health conditions, because they are both linked to cardiovascular disease and renal failure under a wide range of circumstances. Therefore, further research is required to better investigate this correlation in large population studies.

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