

The Importance of a New Cardiovascular Risk Factor – Asymmetric Dimethylarginine

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ABSTRACT

In the past years, scientific research has highlighted the presence of a new cardiovascular risk factor, the implications of which have not been sufficiently studied so far. It is different from conventional risk factors because it acts independently at the endothelial level, having important proatherogenic properties. Through its action, this risk factor leads to increased oxidative stress and promotes the onset of atherosclerosis faster than other well-known risk factors so far. Asymmetric dimethylarginine (ADMA) is a methylprotein that arises from posttranslational methylation of proteins. Its importance has emerged in recent years, when the rate of cardiovascular mortality among patients with chronic kidney disease has been high. The distinctive element of this risk factor compared to other well-known ones is given by its ability to compete directly with nitric oxide synthase, being its strongest endogenous inhibitor, with strong proatherogenic attributions. Given that ADMA has tight correlations with atherogenesis and endothelial damage, its assessment should be taken into consideration for any patient who has been recently diagnosed with high blood pressure.

Keywords: asymmetric dimethylarginine, nitric oxide, proatherogenic, cardiovascular.

Discovery of asymmetric dimethylarginine and its synthesis *in vivo*

Asymmetric dimethylarginine (ADMA) is a methylprotein with important involvement in multiple pathologies and it was discovered in the 1970s by two Japanese scientists (1). Asymmetric dimethylarginine is derived from the catabolism of proteins containing methylated arginine residues. These proteins are involved in translational control and RNA processing. In order to be processed, asymmetric dimethylargi-

nine requires the intervention of an enzyme, named protein-arginine methyltransferase I, which methylates arginine residues. At the same time, another protein, protein-arginine methyltransferase II (2), forms symmetrical dimethylarginine, being the ADMA stereoisomer. The difference between the two methyl proteins is underlined by the fact that ADMA plays a direct role in nitric oxide production, while symmetrical dimethylarginine (SDMA) does not possess this quality. Both asymmetric dimethylarginine and

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symmetric dimethylarginine compete not only with each other, but also with arginine for the cellular transport of nitric oxide. Thus, elevated plasma concentrations of asymmetric dimethylarginine interfere with the intercellular transport of L-arginine, which in turn will lead to decreased nitric oxide production by inhibiting its synthase (3).

Degradation of asymmetric dimethylarginine *in vivo*

Some of the asymmetric dimethylarginine is excreted in the urine, and its catabolism is done under the action of an enzyme called dimethylarginine dimethylaminohydrolase (DDHA). Two isoforms of DDHA have been identified: DDHA I, which is found in tissues where neuronal nitric oxide synthase is expressed, and DDHA II in tissues containing the endothelial isoform of nitric oxide synthase (4). Thus, *in vivo*, under the action of DDHA I, a continuous metabolism of ADMA takes place, which results in dimethylamine and citrulline. Certain pathologic factors may lead to an increased oxidative stress in endothelial cells, consequently leading to a decrease in DDHA I activity and a plasmatic rise of ADMA at the same time.

A higher plasmatic concentration of ADMA will lead to a decreased bioavailability of nitric oxide by inhibiting its synthase, making it the most potent endogenous inhibitor of nitric oxide production. Studies to date have highlighted the negative impact of a slight increase in plasmatic asymmetric dimethylarginine, which is sufficient to inhibit nitric oxide synthesis, thus exacerbating cardiovascular events (5). Higher plasmatic levels of asymmetric dimethylarginine impair the ratio between the factors that provide cardiovascular protection and those that promote the process of atheromatosis. Studies performed on asymptomatic patients have shown that higher plasmatic levels of ADMA were correlated with subclinical vascular disease. Asymmetric dimethylarginine has a normal range between 0.22 and 0.69 $\mu\text{mol/L}$ in healthy subjects (6).

Multiple additional prospective clinical trials are currently ongoing in various patient populations, targeting people with congestive heart failure, high blood pressure, pulmonary hypertension and myocardial infarction in order to determine the pathology with the highest ADMA

concentrations (7). In conclusion, a growing number of prospective clinical trials have shown that the association between high plasmatic levels of ADMA and cardiovascular events extends to various patient groups, leading to a higher mortality rate and poor life quality (8).

Side effects of asymmetric dimethylarginine in cardiovascular pathology

At the beginning of the discovery of asymmetric dimethylarginine, elevated serum concentrations have been reported in patients with chronic kidney disease. Subsequently, researchers studied its involvement in other pathologies, emphasizing its importance in the process of early atherosclerosis, dyslipidemia, diabetes, hypertension and even hyperhomocysteinemia. Regarding atherosclerosis, ADMA has a key role in endothelial dysfunction, being closely related to coronary heart disease, stroke and peripheral arterial disease. Its serum level is directly associated with the intima-media thickness of the carotid arteries (9).

Relationship between asymmetric dimethylarginine and renal impairment

The kidneys have an important role in the metabolism of this dimethylarginine, some of it being excreted at this level. High concentrations of ADMA are present in this particular situation as well, once the renal disease made its debut. In patients with chronic kidney disease, the metabolism of this aminoacid is affected due to abnormal synthesis and excretion. These patients have increased cardiovascular morbidity and mortality. The first study highlighting the involvement of asymmetric dimethylarginine in atherosclerosis was performed in patients with chronic end-stage renal disease (10). The conventional risk factors studied until now play a certain role in mortality and morbidity among patients with end-stage renal disease, but ADMA is a new risk factor that, unlike others known so far, acts in an independent way. Patients with chronic kidney disease have an increased prevalence of cardiovascular disease, the most common being heart failure, peripheral arterial disease, hypertension; the cardiovascular mortality is much higher in these patients. Asymmetric dimethylarginine acts as an independent cardiovascular risk factor, and its increased plasma presence is strongly associ-

ated with the progression of chronic renal disease (11). In patients with end-stage chronic renal disease, a pro-oxidative environment is created, therefore the protein turnover is increased, the plasma level of DDAH decreases by reduction of the tubular mass and consequently, ADMA is no longer excreted through kidneys. Thus, plasma accumulated ADMA will inhibit the synthesis of nitric oxide with its subsequent reduction, resulting in inflammation and oxidative stress, which are key elements of kidney disease progression. The presence of ADMA affects the glomerular filtration rate, amplifying proteinuria, interstitial and glomerular fibrosis (12).

CONCLUSIONS

The distribution of arginine and methyltransferases in the human body can substantially contribute to ADMA elevation due to increased protein turnover. ADMA is the most potent endogenous inhibitor of nitric oxide synthase, leading to endothelium damage and creating a pro-

atherogenic state *in vivo* (13). Consequently, endothelial dysfunction occurs, leading to a higher cardiovascular risk, while simultaneously affecting the integrity of the renal system. ADMA has a pivotal role in the onset of cardiovascular and renal diseases, causing early vascular damage (14); for this reason, a careful monitoring of its plasmatic concentration would be essential in preventing cardiovascular events. At the same time, it is essential to monitor renal function in any hypertensive patient because, when this is affected, the plasmatic level of asymmetric dimethylarginine begins to increase. As a consequence, in order to prevent the overlap between cardiovascular and renal pathology and to promote a better quality of life for our patients, we aim to consider, as a screening method, the dosage of asymmetric dimethylarginine in newly diagnosed hypertensive patients and any patient with a history of cardiovascular disease. □

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