Asymmetric Dimethylarginines

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Asymmetric dimethylarginine (ADMA) is the most potent endogenous inhibitor of nitric oxide synthase (NOS), with higher levels in patients with end-stage renal disease (ESRD). ADMA has shown to be a significant predictor of cardiovascular outcome and mortality among dialysis patients.

ADMA cardiovascular chronic kidney disease

1. Introduction

Asymmetric dimethylarginine (ADMA) and its enantiomer, symmetric dimethylarginine (SDMA), are naturally occurring amino acids that are generated intracellularly. They are post-translationally modified forms of arginine generated during normal protein turnover and were first isolated in human urine in 1970 by Kakimoto and Akazawa [1]. Since then, there have been numerous publications on these two molecules and their relationship with various diseases, especially with cardiovascular diseases. ADMA is the most potent endogenous inhibitor of nitric oxide synthase (NOS) and, therefore, inhibits the production of nitric oxide (NO), which is a key regulator of vascular tone. It has been shown to have a key role in endothelial dysfunction, as well as in the progression of atherosclerosis, and hence in cardiovascular disease. ADMA levels are higher in patients with end-stage renal disease (ESRD) compared to healthy individuals [2]. Among dialysis patients, ADMA may be a significant predictor of cardiovascular outcome and mortality [3]. On the other hand, although initially SDMA was thought to be an innocuous molecule, we now know that it is an outstanding marker of renal function, with patients with ESRD on dialysis showing the highest SDMA levels [4]. Both ADMA and SDMA are considered uremic toxins by the European Uremic Toxin Work Group (EUTox) [5].

2. ADMA, Mortality and Cardiovascular Disease

Cohort studies in patients with CKD and in general population showed a strong and independent link between ADMA, all-cause mortality and cardiovascular events [3][6].

There seems to be a strong association between levels of ADMA and prevalent CVD, and a weaker association with all-cause and CVD mortality in patients with nondiabetic CKD (stages 3 to 4) [7]. However, in the same study the researchers did not find any association with kidney failure or the composite outcome [7].

In their meta-analysis, Schlesinger et al. [8] confirmed a strong association between ADMA and all-cause mortality, with an approximately 50% increased risk of all-cause mortality in patients with higher ADMA levels, especially in

critically ill patients, with a non-linear relation between ADMA and all-cause mortality [8].

When analyzing CVD, they observed a risk increase of 33% in patients with higher ADMA levels, with a positive association between ADMA and CVD [8].

3. ADMA and Chronic Kidney Disease

It is known that ADMA is significantly increased in ESRD [9], as well as in hypertension, adverse cardiovascular events [3][10][11][12], progression of kidney failure [13], renal fibrosis [14], and mortality [3].

In 1992, Vallance et al. showed that patients with ESRD on hemodialysis had higher ADMA levels than controls [2]. Among the ESRD patients on dialysis, ADMA seems to predict cardiovascular outcome and mortality [3].

Investigations have found that NO synthesis is inhibited in patients with end-stage renal disease (ESRD) and that ADMA is capable of inhibiting NO production in vivo and in vitro [2], which may result in vasoconstriction, hypertension and immune dysfunction, among other outcomes. We also know that increased ADMA levels are also associated to other cardiovascular risk factors such as increased plasma levels of low-density lipoprotein cholesterol, triglycerides, glucose, homocysteine, and mediators of inflammation [15].

There are studies, however, which refer to the association between treatment with erythropoietin (EPO) and ADMA levels. Scalera et al. found that in vitro EPO post-translationally impairs DDAH activity via increased oxidative stress and that endothelial cells responded to EPO by increasing the production of ADMA in a dose-dependent manner [16]. Although EPO has important beneficial effects in the correction of anemia, it has also been observed that it may have side effects, such as an increase in blood pressure (BP) and alteration in the production of nitric oxide in endothelial cells, thus increasing oxidative stress [17]. Again, Scalera et al. observed in patients with CKD, who received treatment with EPO for the first time, that there was an increase in plasma ADMA levels [16]. More recently it has been observed that erythrocyte ADMA accumulation may suppress erythropoietin receptor expression, contributing to impaired response to EPO in pre-dialysis patients [18].

4. ADMA and Dialysis

Because ADMA, like urea, has a low molecular weight, dialysis seems to be the best option for the elimination of ADMA in patients with CKD [19]. However, studies that have evaluated the impact of hemodialysis (HD) on plasma ADMA concentrations show that this view is too simplistic, since the reduction of ADMA does not necessarily translate to a subsequent clinical significance [19]. Some studies have shown a significant decrease in plasma ADMA concentrations with HD, which ranged from 23% [10] to 65% [20]. However, other studies did not find a significant decrease in ADMA levels post-dialysis [9][21][22]. The data suggest that dialysance, and therefore the elimination of ADMA by dialysis, is hampered by the fact that ADMA is bound to plasma proteins [22]. Only about 12% of the amount of ADMA produced per day was detected in the dialysate after a standard HD [22]. Although

there are small studies suggesting that high-flux membranes and hemodiafiltration [23] may be more efficient to eliminate ADMA, this has not been confirmed [24][25].

5. ADMA and Hypertension

Regarding the relationship between ADMA and hypertension, there is increasing evidence that NO plays a relevant role in the regulation of vascular tone and BP [26][27]. Two possible mechanisms might explain how ADMA participates in the pathogenesis of hypertension. On the one hand, ADMA, through the inhibition of endothelial NOS activity, can exert a vascular vasoconstrictor effect [28][29]. On the other hand, ADMA can inhibit the renal excretion of sodium by reducing renal NO synthesis [30][31][32]. Kielstein et al. showed that exogenous ADMA increases systemic vascular resistance, as well as mean arterial pressure, and reduces cardiac output in men [12]. In this study, the administration of ADMA dose-dependently impaired renal blood flow and sodium reabsorption.

In rats undergoing 5/6 nephrectomy, ADMA levels are clearly related to BP levels [33]. In human Japanese subjects without coronary artery disease or peripheral arterial disease, it has been observed that plasma levels of ADMA are associated with higher mean BP levels [34]. This relationship seems to be more evident in patients with essential hypertension [35][36][37], especially in those individuals who are salt sensitive [38]. ADMA is probably the most important regulator of NO in the kidney [39]. A high intake of salt increases the urinary excretion of ADMA [40] and also increases the expression of all isoforms of NOS in the renal medulla [41]. On the other hand, BP itself can raise plasma ADMA levels through the positive regulation of protein arginine methyltransferases (PRMTs) by an increase in shear stress through the NFκB pathway [42]. Plasma levels of ADMA rise in response to an expansion of extracellular volume. Thus, in hypertensive patients, in the presence of salt overload, an increase in ADMA levels and a decrease in NO levels can be observed [38]. Likewise, angiotensin II and the generation of reactive oxygen species (ROS) may also be involved in the elevation of ADMA levels in hypertension [43]. This correlation between hypertension and ADMA levels is quite clear in subjects with essential hypertension or with some degree of CKD, where the regulation of BP through the kidneys is still preserved. However, in hemodialysis patients without residual renal function, we do not have reliable data about the relationship between ADMA and hypertension.

6. ADMA and Ageing

Several studies have found that plasma ADMA levels increase with age [34][44][45]. Some authors point out the possibility that ADMA increases with age due in part to the decrease in GFR associated with ageing [39][44]. Interestingly, an in vitro study demonstrated that ADMA increases the rate of endothelial senescence and shortens the telomere length by means of a significant reduction in telomerase activity in endothelial cells treated with ADMA, in comparison with the control group [46]. The authors concluded, therefore, that ADMA accelerates ageing and may increase oxidative stress in endothelial cells.

7. ADMA, Endothelial Dysfunction and Inflammation

Endothelial dysfunction measured by ADMA and inflammation has been clearly related to atherosclerosis, cardiovascular events and death in patients with CKD [47]. Inflammation is capable of amplifying the effect of ADMA on the severity of atherosclerosis in patients with CKD [47]. However, if ADMA and inflammation interact, it is still unknown whether this interaction increases the risk of cardiovascular events and death [47]. In a study by Tripepi et al. [47], in a cohort of 225 patients on hemodialysis, it was observed that there was an interaction between biomarkers of inflammation and ADMA, so that mortality was higher in the group that had both elevated ADMA and C-reactive protein (CRP), in comparison with groups that only had one of the markers elevated. The authors concluded, therefore, that inflammation amplifies the risk of death and cardiovascular events in patients with high ADMA levels in subjects on hemodialysis [47]. Other studies show that endothelial dysfunction is associated with chronic inflammation [48][49]. In patients with type 2 diabetes mellitus, an interaction between CRP and ADMA was observed in a prospective cohort study, which was also related to cardiovascular events [50].

Inflammation in patients with CKD is a multifactorial problem [51], since both factors related to dialysis and factors independent of it can favor inflammation by stimulating the synthesis or release of proinflammatory cytokines such as PCR, IL-1, IL-6, TNF-α, and IFN-γ [49].

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