

Endothelium, asymmetric dimethylarginine, and atherosclerosis in chronic kidney disease

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The endothelium is not just a simple inert semi-permeable structure, which merely serves to line blood vessels. Strategically located between the vascular smooth muscle cells in the blood vessel walls and the blood stream, it forms an active organ with endocrine and paracrine functions. It is also the organ with the largest surface area in the human body, which contains approximately 10^{13} endothelial cells weighing about 1 kg and covering a surface area of 4000 to 7000 m², equivalent to a football playground. The endothelial cell monolayer forming the inner lining of all blood vessels within the vascular tree, covering glycocalyx, and the underlying basement membrane constitute the endothelium.

In 1980, Furchgott and Zawadzki¹ discovered that acetylcholine requires the presence of endothelial cells to elicit vasodilation. Since then, there have been enormous advances in our understanding of the biology of the endothelial cell. Now we know that this is largely a result of a vasodilatory endothelium-derived nitric oxide (NO), and to a lesser extent of prostacyclin, different endothelium-derived hyperpolarizing factors, and C-type natriuretic peptide. Moreover, the endothelium secretes several vasoconstrictory substances including thromboxane A₂, endothelins, angiotensin II, and reactive oxygen species. Inflammatory modulators include adhesion molecules like intercellular adhesion molecule 1, vascular adhesion molecule 1, E-selectin, NO, and nuclear factor κB. Endothelium modulates hemostasis by releasing plasminogen activator, its type 1 inhibitor, von Willebrand factor, NO, prostacyclin, thromboxane A₂, tissue factor pathway inhibitor, and fibrinogen.² Since the endothelium regulates the balance between pro- and antithrombotic activities, in the quiescent state, NO and prostacyclin directly inhibit platelet aggregation, and thrombomodulin inactivates thrombin. Under basal conditions, the endothelium maintains the vessel in a relatively dilated state. However, the endothelium has the capacity

to respond to various physiological stimuli, such as shear stress, temperature, or sympathetic activation. In response to these stimuli, on the one hand the endothelium becomes prothrombotic, secreting platelet-activating factor and expressing thromboplastin on cell membranes, but on the other hand blood vessels dilate in a process called flow-mediated dilation.³

NO produced by endothelial cells through the endothelial NO synthase (eNOS) pathway plays a major role in the maintenance of endothelial function, and NO synthesis leads to vasoconstriction if the endothelium is removed or dysfunctional. It also exhibits many other effects, such as inhibition of platelet adhesion and aggregation, the effect that may be synergistic with that of prostacyclin, as well as a reduction in endotoxin- and cytokine-induced expression of tissue factor and the prothrombotic potential of the endothelial cell, and finally, inhibition of monocyte adhesion to the endothelium.

In the past, the major focus of researchers was on the measurement of endothelium-derived vasoactive substances, inflammatory markers, or adhesion molecules. One of the reasons for such limited clinical understanding of the endothelium is that the endothelial "organ" is hidden and inaccessible. Blood sample assessment could represent only the net result of activity from multiple vascular beds, whereas localized "hot spots" in the specific sites of the vasculature could be overlooked. Investigators have attempted to assess the endothelium status and to quantify the risk of atherosclerosis.

The production and bioavailability of NO largely contribute to endothelial dysfunction in thrombosis, hypertension, atherosclerosis, and diabetes.² eNOS was shown to be a major NOS enzyme in the renal vasculature. Asymmetric dimethylarginine (ADMA) is an endogenous amino acid similar to L-arginine and is able to inhibit eNOS. ADMA is associated with impaired NO synthesis and is considered a strong predictor of cardiovascular

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Received: March 10, 2018.
Accepted: March 12, 2018.
Published online: March 29, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018;
128 (3): 145-147
doi:10.20452/pamw.4232
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Kraków 2018

events and death in patients with chronic kidney disease (CKD) and in the general population.

Lindner et al⁴ first drew attention to the excessive incidence of atherosclerotic cardiovascular mortality in hemodialyzed patients with uremia. Endothelial cell damage or injury is invariably associated with such clinical conditions as thrombosis, hypertension, renal failure, and atherosclerosis and may be also responsible for accelerated atherosclerosis in patients with chronic renal failure. On the one hand, CKD may be a part of a sub-clinical, generalized atherothrombosis, while on the other hand, an impairment of kidney function is responsible for the creation of atherogenic milieu. High oxidative stress and increased levels of the endogenous NO synthase inhibitor, ADMA, was reported to be a novel risk factor for endothelial dysfunction.⁵

Serum ADMA levels in CKD increase due to defective inactivation and excretion. High ADMA levels are associated with endothelial dysfunction, as well as with higher intima-media thickness and cardiovascular events in CKD.⁶ Moreover, Ravani et al⁷ reported that high ADMA levels represent a strong independent risk factor for progression of CKD. However, it is still an open question of cause and effect, whether it is a result of impaired kidney function or whether it merely reflects vascular disease, which is highly prevalent in CKD or end-stage kidney disease, since both proinflammatory markers and biochemical markers of endothelial dysfunction are increased in CKD. In this respect, reduced NO synthesis by endothelial cells due to accumulation of endogenous inhibitors of the NOS such as ADMA has been accused of accelerating progression of endothelial dysfunction. It was emphasized by Brunet et al⁸ in their review on uremia and vascular dysfunction. Thus, reducing blood ADMA levels could be potentially beneficial in clinical trials aimed at reducing the loss of kidney function in patients with CKD.⁹

Coen et al¹⁰ explored also a possible relation between ADMA and serum parathyroid hormone (PTH) levels, and found that ADMA levels could be influenced by the severity of hyperparathyroidism and contribute to cardiovascular death linked to PTH of hemodialysis patients. In their study, which included 79 patients on hemodialysis, ADMA was related to total and coronary calcium volumes, hemodialysis vintage, body mass index, cholesterol, serum albumin, PTH, natural logarithm of PTH, and bone alkaline phosphatase. They concluded that the strong positive correlation between ADMA and natural logarithm of PTH, validated by the regression analysis, may suggest a link between ADMA and PTH-derived vascular damage. ADMA levels could be influenced by the severity of hyperparathyroidism and contribute to PTH-related cardiovascular death of hemodialysis patients.

In their previous paper, Janda et al¹¹ assessed the relationship between selected clinical and biochemical parameters of patients with end-stage renal disease and arterial calcification. They found

that calcification of the radial artery was associated with a higher prevalence of impaired fasting glucose and diabetes, older age, as well as higher osteoprotegerin and serum ADMA concentrations. During a 3-year follow-up, they reported that 16 patients (47%) with calcifications in the radial artery died, while in the group without calcifications there were only 3 deaths (12%). All other deaths occurred due to cardiovascular causes. This confirmed the previous findings of Ogawa et al,¹² who demonstrated that cardiovascular mortality was significantly higher in patients with aortic arch calcification assessed by computed tomography in a cohort of 401 patients on hemodialysis during a 4-year follow-up.

In this issue of the *Polish Archives of Internal Medicine (Pol Arch Intern Med)*, Krzanowski et al¹³ evaluated the correlation between ADMA levels, radial artery calcification, and common carotid intima-media thickness (CCI-IMT) in 51 patients with CKD, in whom arteriovenous fistula for hemodialysis access was created, allowing a collection of radial artery samples for histological examination, and in 33 healthy volunteers. They found that patients with calcifications in the radial artery had significantly higher ADMA levels. In logistic regression, ADMA positively predicted the presence of radial artery calcifications independently of age, hemodialysis status, the Framingham risk score, and serum pentraxin 3 levels. In addition, serum ADMA levels higher than the median were associated with older age and higher serum levels of phosphate, calcium and phosphate product, fibroblast growth factor 23, osteoprotegerin, osteopontin, pentraxin 3, soluble receptor of soluble necrosis factor receptor II, matrix metalloproteinase 2, and thrombomodulin. Interestingly, calcifications of the radial artery revealed by alizarin red staining, especially those with grades 1 to 3, were also more common in patients with ADMA levels above the median as well as atherosclerotic plaques in the common carotid artery. In more advanced stages of CKD, there was also a positive association between circulating ADMA levels and risk of medial arterial calcification. It should be emphasized that patients with most advanced calcifications (alizarin red staining grade 4) had relatively low ADMA levels. It might be due to the fact that calcium deposition following endothelial cell injury by ADMA occurred earlier and then progressed even in patients with low ADMA levels but higher milieu of other substances enhancing calcification. As underlined by the authors, the relationship between circulating ADMA levels and vascular calcification assessed histologically has not been studied yet; however, some data were published on the relationship between ADMA and vascular calcification assessed by imaging studies.

In a recent systematic review and meta-analysis, Wang et al¹⁴ evaluated the possible correlations between ADMA and CCI-IMT in patients with CKD. They searched PubMed, Cochrane Library, and EMBASE electronic databases and selected 6 articles. After reviewing the overall

pooled estimate of the correlation coefficient, they concluded that ADMA levels in patients with CKD were positively related to CCI-IMT. Thus, ADMA may serve as a predictor of early-onset atherosclerosis and atherosclerotic disease in this vulnerable population. It is of utmost importance as ADMA per se seems to be responsible for a 52% increase in the risk of death and for a 34% increase in the risk of cardiovascular events in patients on dialysis.¹⁵

NOTE The opinions expressed by the authors are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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