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Arginine, dimethylated arginine and homoarginine in relation to cardiovascular risk in patients with moderate chronic kidney disease

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ABSTRACT

Objectives: Arginine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), arginine/ADMA ratio and homoarginine could potentially affect nitric oxide production and have been studied in relation to cardiovascular risk (CVR) in various clinical populations. Prospective studies on the CVR associated with arginine/ADMA ratio and homoarginine in patients with moderate chronic kidney disease (CKD) are still scarce. We have studied how arginine, homoarginine and dimethylated arginine can predict cardiovascular events in such a population.

Design and methods: We measured plasma concentrations of arginine (P-arginine), ADMA (P-ADMA), SDMA (P-SDMA), homoarginine (P-homoarginine) and other covariates in 160 patients with predialytic CKD (mean age 57 years and mean eGFR 43 mL/min/1.73 m^2) and followed them for 58 months in median. The risks of fatal and non-fatal cardiovascular events associated with the predictors were evaluated with multivariable Cox proportional hazard analysis.

Results: There were 31 cardiovascular events during the observation period. In a multivariable model adjusted for age, sex, previous cardiovascular disease, P-cystatin C and P-homoarginine, the hazard ratio (HR) associated with an increase in arginine/ADMA ratio by 10 was 0.83 ($P = 0.03$). The HR of a 1 μmol/L increase in P-homoarginine in the same model was 1.78 ($P = 0.01$). A statistically significant interaction between P-homoarginine and P-cystatin C was found in an extended multivariable model. P-SDMA was not associated with increased CVR after adjustment for basic covariates.

Conclusion: This study demonstrates a negative association between arginine/ADMA ratio and CVR in CKD patients and a positive association between P-homoarginine and CVR. The latter is in contrast to what has been demonstrated by others.

Introduction

Patients with chronic kidney disease (CKD) have increased risk of cardiovascular events and increased mortality and the increased risk is only partly explained by traditional cardiovascular risk (CVR) factors [1,2]. Endothelial dysfunction is thought to play an important role in the proceeding pathophysiological processes [2]. Asymmetric dimethylarginine (ADMA) has been known for several years as an endogenous inhibitor of nitric oxide (NO) production. ADMA is a competitor to arginine, the substrate used by nitric oxide synthase (NOS) to produce NO [3]. NO is a potent vasodilator and has important effects as a mediator of antithrombotic processes, growth inhibition and inflammation [4]. In various clinical populations, ADMA has been shown to be a predictor and a risk factor for cardiovascular events and overall mortality [5–7]. Patients with CKD have elevated plasma concentrations of ADMA (P-ADMA) primarily because of a reduced elimination by the enzyme dimethylarginine dimethylaminohydrolase (DDAH), but maybe also because of an increased methylation of arginine as a consequence of increased protein methyltransferase (PRMT) gene expression [8]. Because ADMA is a competitor to arginine, the arginine/ADMA ratio is an interesting risk marker to study. Perhaps it could be used to select patients that might benefit from arginine supplementation [9]. The arginine/ADMA ratio has not been as extensively studied as ADMA in prospective population studies of CVR.

Symmetric dimethylarginine (SDMA) is a second dimethylated arginine variant that might inhibit NO-production due to its competition to arginine for transportation into the cell [10]. Plasma concentration of SDMA (P-SDMA) has also been studied as a CVR marker [11,12], although in patients with renal failure, P-SDMA is primarily a marker of renal function [13].

Lately homoarginine, a homolog of arginine, has come up as a new potential risk modulator, but the exact effect of homoarginine on the cardiovascular system is unknown. Homoarginine can be used as a

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Table 1
Characteristics on the population.

Variable	Entire population	With event	Without event
	N = 160	N = 31	N = 129
Demographic factors			
Male gender (%)	70	68	71
Age (y) mean (SD)	56.9 (17.3)	68.7 (11.1)	54.1 (17.3)
CVD risk factors			
Previous CVD (%)	29	71	19
Current smoker (%)	18	6	21
Diabetes n (%)	19	32	16
Diagnosed hypertension (%)	60	65	59
Systolic BP (mmHg) mean (SD)	129 (16.0)	137 (18.2)	128 (15.0)
Diastolic BP (mmHg) mean (SD)	77 (10.0)	76 (11.0)	78 (9.7)
Body mass index (kg/m^2) mean (SD)	27.3 (5.3)	26.8 (4.4)	27.4 (5.5)
Estimated GFR in mL/min/1.73 m^2, mean (SD)*	43 (27)	29 (13)	47 (28)
Biochemical factors			
P-cystatin C (mg/L) mean (SD)	2.05 (0.83)	2.61 (0.92)	1.91 (0.75)
B-haemoglobin (g/dL) mean (SD)	13.5 (1.6)	13.0 (1.6)	13.6 (1.6)
S-total cholesterol (mmol/L) mean (SD)	4.9 (1.2)	5.0 (1.4)	4.9 (1.2)
S-HDL cholesterol (mmol/L) mean (SD)	1.3 (0.4)	1.2 (0.3)	1.3 (0.5)
S-triglycerides (mg/dL) mean (SD)	2.1 (1.2)	2.1 (1.1)	2.0 (1.3)
B-HbA1c (%) mean (SD)	6.1 (0.88)	6.4 (1.0)	6.0 (0.8)
P-homocysteine (μmol/L) mean (SD)	20.5 (8.7)	22.7 (9.0)	19.9 (8.6)
S-PTH (pmol/L) median (range)	7.5 (0.4–59)	10.8 (0.4–55)	6.8 (1.8–59)
P-CRP (mg/L) median (range)	2.2 (0.01–148)	5.3 (0.6–27)	1.8 (0.01–148)
S-albumin (g/L) mean (SD)	42 (4.3)	41 (4.6)	42 (4.2)
S-ionized calcium (mmol/L) mean (SD)	1.23 (0.05)	1.21 (0.05)	1.23 (0.05)
P/S-phosphate (mmol/L) mean (SD)	1.09 (0.26)	1.14 (0.30)	1.08 (0.25)
S-uric acid (μmol/L) mean (SD)	413 (105)	431 (99)	408 (106)
U-albumin/creatinine ratio (mg/mmol) median (range)	13 (0.2–888)	7.8 (1.0–888)	14 (0.2–467)
P-ADMA (μmol/L) mean (SD)	0.71 (0.11)	0.77 (0.11)	0.70 (0.12)
P-Homoarginine (μmol/L) mean (SD)	1.98 (0.85)	2.01 (0.94)	1.97 (0.83)
P-SDMA (μmol/L) mean (SD)	1.1 (0.45)	1.3 (0.51)	1.0 (0.42)
P-arginine (μmol/L) mean (SD)	72.6 (21.0)	68.4 (16.9)	73.6 (21.8)
P-arginine/ADMA ratio mean (SD)	103 (31)	89 (20)	107 (32)
Medication			
RAAS inhibitors[a] (%)	74	68	75
Platelet inhibitors[b] (%)	23	61	14
Other antihypertensives[c] (%)	51	74	45
Statins (%)	51	81	43

Baseline characteristics of the entire population and for those with and without a cardiovascular event separately. Data are given as mean (standard deviation) and frequencies (%) for continuous and dichotomous variables respectively. Very skewed continuous variables are given as median (range).

[a] RAAS inhibitors means treatment with renin angiotensin aldosterone inhibitors.

[b] Platelet inhibitor means treatment with acetylsalicylic acid, clopidogrel or Gp2a/3b-inhibitors.

[c] Other antihypertensives means treatment with beta blockers, alpha blockers and calcium channel blockers.

* Estimated according to the MDRD-formula.

non-optimal substrate for NO-production by NOS and the kidneys are involved in homoarginine synthesis [14]. Both a protective and a possibly harmful effect of elevated plasma concentration of homoarginine (P-homoarginine) have been proposed [14–16]. Further investigations on this relation have been demanded [14]. Reports on CVR associated with P-homoarginine in patients with CKD are scarce; however, a recent published paper by Ravani et al. [17] demonstrated an inverse relation between P-homoarginine and overall mortality in such patients. A potentially important interaction between P-homoarginine and renal function in relation to CVR has also recently been proposed [18].

In a previous study [19], we have described factors (established cardiovascular risk factors, biochemical analysis, medications etc.) that could predict plasma concentrations of arginine, ADMA, and arginine/ADMA ratio in CKD patients. In the present study, we have investigated the risk of fatal and non-fatal cardiovascular events associated with plasma concentrations of ADMA, SDMA, arginine, homoarginine and arginine/ADMA ratio in the same CKD population.

Subjects and methods

Population

The study population of 160 patients with predialytic CKD has previously been described in detail [19]. Characteristics of the whole population are summarized in Table 1 as well as characteristics of the patients that experienced, and not experienced a cardiovascular event in this follow-up study. Patients were included if they had a diagnosis of CKD and were seen by a nephrologist on a regular basis. The patients underlying renal disease as previously presented in [19], were primary glomerular disease (glomerulonephritis) in 41%, tubulointerstitial renal disease (interstitial nephritis, polycystic kidney disease, chronic pyelonephritis, nephrocalcinosis, sarcoidosis, postrenal disease etc.) in 21%, nephrosclerotic disease (nephrosclerosis and hypertensive kidney disease) in 21%, systemic inflammatory disease (Wegner granulomatosis, systemic vasculitis, SLE) in 9% and diabetic kidney disease in 8%. The patients were included between February 2007 and February 2009. The median time of follow-up was 58 months (min-max 0.5–61). Four