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Asymmetric Dimethylarginine (ADMA) Levels Are Lower in Hemodialysis Patients Treated With Paricalcitol

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Introduction: Chronic kidney disease is a major public health problem. In the last decade, it has been shown that the early stages of chronic kidney disease are associated with an inflammatory condition involving an increased risk of cardiovascular morbidity and long-term mortality. In patients with chronic kidney disease and more specifically those on hemodialysis, cardiovascular events are the most common cause of death. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase and may be an independent risk factor for endothelial dysfunction and cardiovascular disease.

Methods: We performed a cross-sectional analysis to identify factors that were associated with ADMA such as certain medications related to cardiovascular disease in dialysis patients.

Results: Patients who were treated with paricalcitol had significantly lower levels of ADMA (0.21 $\pm$ 0.19 μmol/l) compared with those not treated with paricalcitol (0.42 $\pm$ 0.35 μmol/l) ($P = 0.00027$). Dividing ADMA levels by quartiles, patients treated with paricalcitol were less likely to have very high level ADMA ($P = 0.014$), whereas there were no significant differences with other medications. Higher dose of paricalcitol was also related to lower levels of ADMA noting an inverse correlation ($r = –0.36$, $P = 0.013$).

Discussion: Hemodialysis patients treated with paricalcitol presented significantly decreased ADMA levels compared with those who did not receive this treatment. Possible beneficial effects in terms of cardiovascular morbidity and mortality by paricalcitol and its association with ADMA and nitric oxide synthesis are unknown. Studies to confirm this effect and determine the underlying pathophysiological mechanism are necessary.

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Asymmetric dimethylarginine (ADMA) is an endogenous nitric oxide synthase inhibitor that may be an independent risk factor for endothelial dysfunction and cardiovascular disease.[1] Patients with and without established coronary heart disease and elevated levels of serum ADMA have an increased risk of acute coronary events compared with individuals with lower ADMA levels.[2–4] ADMA, which is significantly increased in end-stage renal disease (ESRD),[5] is an endogenous inhibitor of nitric oxide.[6,7] Inhibition of nitric oxide synthesis in patients with ESRD may cause vasoconstriction and hypertension, thereby resulting in adverse cardiovascular outcomes.[8–11] In hemodialysis patients, plasma ADMA is a strong and independent predictor of overall mortality and cardiovascular outcome.[9]

Paricalcitol has demonstrated effects on endothelial function and suppressing inflammation decreasing levels of high-sensitivity C-reactive protein, tumor necrosis factor-α, and interleukin-6 in hemodialysis patients.[12] High ADMA levels are a consequence of endothelial dysfunction[1] and the effects of paricalcitol on ADMA levels have not been reported.

Certain drugs such as proton pump inhibitors have been associated with the elevation of asymmetric

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dimethylarginine levels,[13] whereas other drugs have been associated with a reduction of ADMA levels in several reports, such as certain angiotensin converting enzyme inhibitors and angiotensin receptor blockers,[14–16] metformin,[17] rosiglitazone,[17,18] or rosuvastatin.[19]

We report a study designed to evaluate the relationship between levels of ADMA with survival in hemodialysis patients and a cross-sectional analysis to study the association between levels of ADMA and the use of drugs that have demonstrated a reduction of cardiovascular disease in dialysis patients, such as statins, aspirin, angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers, and paricalcitol.

METHODS

Study Design, Setting, and Patients

We performed a cross-sectional observational study in patients on chronic hemodialysis to evaluate the association of ADMA with medication as well as a prospective study to evaluate ADMA with mortality. The study was performed in the Hospital Universitario de Gran Canaria Doctor Negrin, Gran Canaria, Spain, between April 2011 and April 2014. Ninety-three patients who underwent chronic hemodialysis treatment (62.4% men and 37.6% women) were randomly selected from a total of 231 patients. All patients were being treated 3 times a week with standard bicarbonate dialysis (Na^+ 138 mmol/l, HCO_3^- 35 nnol/l, K^+ 1.5 mmol/l, Ca^{2+} 1.25 mmol/l, Mg^{2+} 0.75 mmol/l) with 1.7 or 2.1 polysulfone membrane dialyzers.

Patients continued with their usual treatment prescribed for chronic diseases previously diagnosed. They had no changes on medication related to CKD bone mineral disease for 2 months before the serum for determination of ADMA levels was collected. No changes were therefore made of paricalcitol or calcitriol from 2 months before. No patients had treatment with calcitriol or alphacalcidol. There were no significant differences between quartiles attending to cinacalcet or phosphate binders (calcium and non–calcium-based phosphate binders).

The protocol adhered to the ethical guidelines of our hospital and this study was evaluated and accepted by the Clinical Research Ethics Committee of the Hospital Universitario de Gran Canaria Doctor Negrin, which meets BPC (CPMP/ICH/135/95) standards and Spanish laws (R.D. 223/2004). All patients enrolled in the study received exhaustive information, and were asked for their participation, signing the corresponding consent.

A review of medical records was conducted, as well as computer databases used in the Nephrology Department to collect data, including demographic, anthropometric, physical examination, vital signs, and biochemical data. At 36 months, a review of death records was conducted. Finally, we proceeded to the statistical analysis of the results.

The variables analyzed are defined in Tables 1 and 2.

Laboratory

Samples of peripheral venous blood were obtained, the first dialysis day of the week (Monday or Tuesday), after a minimum fasting period of 8 hours. Blood samples were sent to the reference laboratory for biochemical determinations. The samples for ADMA determination were kept at –80°C until the analysis of ADMA was performed.

Table 1. Baseline characteristics of patients including totals and quartiles of ADMA levels (μmol/l)

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
Age (yr)	66 (19)	65 (20)	64 (10)	70 (19)	74 (19)	0.15
Sex (men)	Men: 58 (62.4%)	15 (62.5)	14 (60.9)	16 (69.6)	13 (56.5)	0.86
Dry weight (kg)	71.0 ± 13.4	68.3 ± 13.5	70.8 ± 11.8	75.7 ± 12.1	69.5 ± 69.5	0.26
BMI (kg/m^2)	25.7 ± 4.7	24.1 ± 4.3	25.7 ± 5.0	26.9 ± 4.0	26.2 ± 5.0	0.19
BMI ≥ 30 kg/m^2	Yes: 16 (17.2%)	2 (8.3)	4 (17.4)	4 (17.4)	6 (26.1)	0.475
Time in HD (mo)	53.1 (57.9)	46 (80)	46.7 (44.1)	58.2 (61.2)	53.9 (54.8)	0.48
Central venous catheter	15 (16.1%)	1 (4.2)	4 (17.4)	4 (17.4)	6 (26.1)	0.21
Charlson Comorbidity Index	4 (2)	3.5 (2)	4 (2)	5 (2)	3.5 (2)	0.46
Ethiology of CKD	Diabetic nephropathy: 35 (37.6%) Nephroangioesclerosis: 6 (6.5%) Polycystic kidney disease: 10 (10.8%) Glomerulonephritis: 13 (14%) Others: 21 (22.6%) Unknown: 8 (8.6%)	10 (41.7) 1 (4.2) 4 (16.7) 3 (12.5) 5 (20.8) 1 (4.2)	7 (30.4) 0 (0) 3 (13) 5 (21.7) 6 (26.1) 2 (8.7)	8 (34.8) 4 (17.4) 2 (8.7) 3 (13) 4 (17.4) 2 (8.7)	10 (43.5) 1 (4.3) 1 (4.3) 2 (8.7) 6 (26.1) 1 (4.3)	0.82
DM	Yes: 42 (45.2%)	10 (41.7)	11 (47.8)	9 (39.1)	12 (52.2)	0.82
ACEi/ARBs	22 (23.7%)	9 (37.5)	4 (17.4)	5 (21.7)	4 (17.4)	0.348
Paricalcitol	37 (39.8%)	14 (58.3)	11 (47.8)	8 (34.8)	4 (17.4)	0.026
Coronary arterial disease	23 (25.3%)	5 (20.8)	5 (22.7)	6 (26.1)	7 (31.8)	0.87

Data are shown as mean (SD), median (interquartile range), or number of cases (percentage frequency), as appropriate.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HD, hemodialysis.