Indole-3 acetic acid predicts cardiovascular event and mortality in chronic kidney disease patients: evidence for an endothelial inflammatory and prooxidant effect

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INTRODUCTION

Chronic inflammation and oxidative stress are key mechanisms in endothelial dysfunction, atherosclerosis and cardiovascular disease in patients with chronic kidney disease (CKD). Indole-3 acetic acid (IAA) is a protein-bound uremic solute from tryptophan metabolism. Levels of IAA are increased in the serum of CKD patients, but its vascular toxicity has been few studied. We hypothesized that IAA is associated with mortality and cardiovascular events in CKD patients and induces endothelial oxidative stress and inflammation in vitro.

PATIENTS

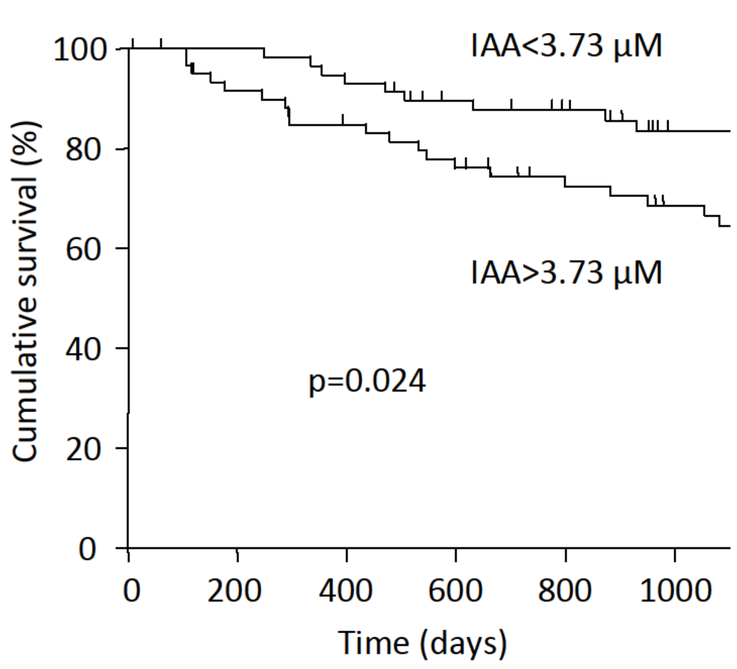
120 patients with CKD were prospectively enrolled. Overall mortality and cardiovascular events were listed during 1100 days. IAA was measured in serum by HPLC. The Kaplan–Meier method was used to estimate the cumulative event-free rate for the time to overall mortality and the first cardiovascular event in patients with IAA level above and below the median (3.73 µM). Multivariate analyses of overall mortality and cardiovascular events were performed using a Cox proportional hazard model with serum IAA as a continuous variable.

Baseline characteristics of the study population

	All patients (n=120)	IAA< 3.73 µM	IAA>3.73 µM
Age (years)	67 (23; 91)	64 (23; 87)	71 (32; 91)*
Gender ratio (W/M)	46/74	25/35	21/39
Body Mass Index (kg/m²)	24.1 (14.3; 47)	24.4 (16.9; 47)	23.7 (14.3; 39.8)
Dialyzed patients (%)	73 (61%)	43%	78%*
eGFR[a] (mL/min/1.73m²)	26 ± 12	28 ± 11	19 ± 13*
Hypertension	110 (92 %)	55 (92%)	55 (92%)
Systolic Blood Pressure (mmHg)	142± 23	145 ± 24	140 ± 23
Diastolic Blood Pressure (mmHg)	76 ± 14	78 ± 14	73 ± 14*
Smokers	48 (40%)	27 (45%)	21 (35%)
History of cardiovascular disease	42 (35%)	16 (27%)	26 (43%)
CRP (mg/L)	5 (0.1; 78)	4 (0.1; 30)	7 (0.1; 78)**
Hemoglobin (g/dL)	12 ± 1.4	12 ± 1.6	11.9 ± 1.2
Albumin (g/L)	36 ± 4	35.9 ± 3.4	36 ± 4.6
Calcium (mmol/L)	2.33 (1.84; 2.66)	2.34 (2.06; 2.55)	2.32 (1.84; 2.66)
Phosphate (mmol/L)	1.28 (0.54; 3.17)	1.22 (0.65; 2.91)	1.44 (0.54; 3.17)
Cholesterol (mmol/L)	4.79 ± 1.26	4.94 ± 1.33	4.63 ± 1.17
LDL-cholesterol (mmol/L)	3.09 ± 1.08	3.02 ± 1.11	3.18 ± 1.06
Triglycerides (mmol/L))	1.44 (0.37; 5.96)	1.65 (0.37; 5.96)	1.22 (0.37; 3.67)*
Malondialdehyde (nmol/L)	200 (100; 500)	150 (100; 500)	215 (120; 430)**
IAA (µmol/L)	3.73 (0.6; 18.58)	1.86 (0.6; 3.71)	6.67 (3.75; 18.58)***

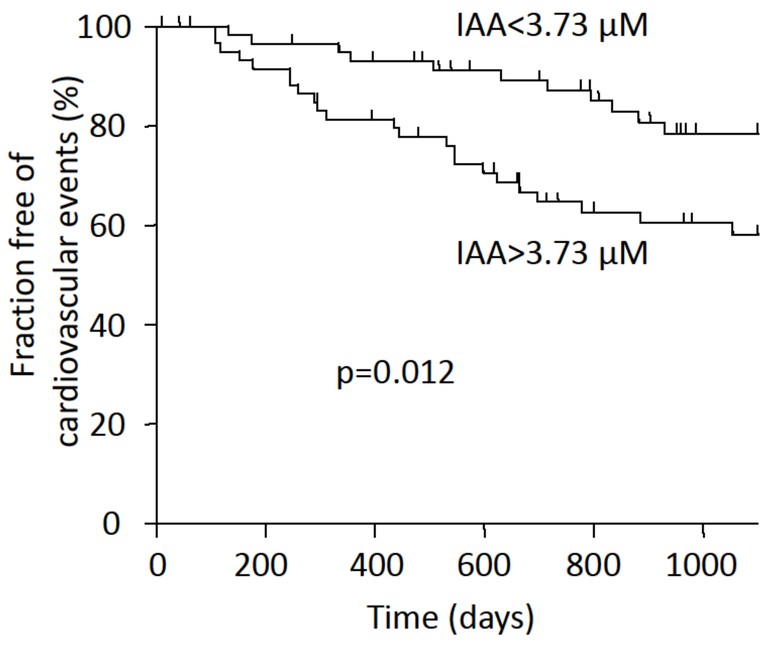
[a] calculated with MDRD formula for non-dialyzed CKD patients
Results are given as mean ± SD, or in median (min;max)
* p<0.05, **p<0.01, ***p<0.001 compared to patients with IAA levels <3.73 µM

IAA predicted the risk of death in patients with CKD



Models of patient survival (event 29/120)	RR	95% CI	p
Unadjusted	2.44	1.34 to 4.46	0.004
Model 1 [a]	1.95	1.05 to 3.65	0.036
Model 2 [b]	2.19	1.15 to 4.14	0.017
Model 3 [c]	2.01	1.01 to 4.00	0.047
Model 4 [d]	2.09	1.11 to 3.93	0.022
Model 5 [e]	2.46	1.35 to 4.50	0.003

IAA predicted the risk of cardiovascular events in patients with CKD



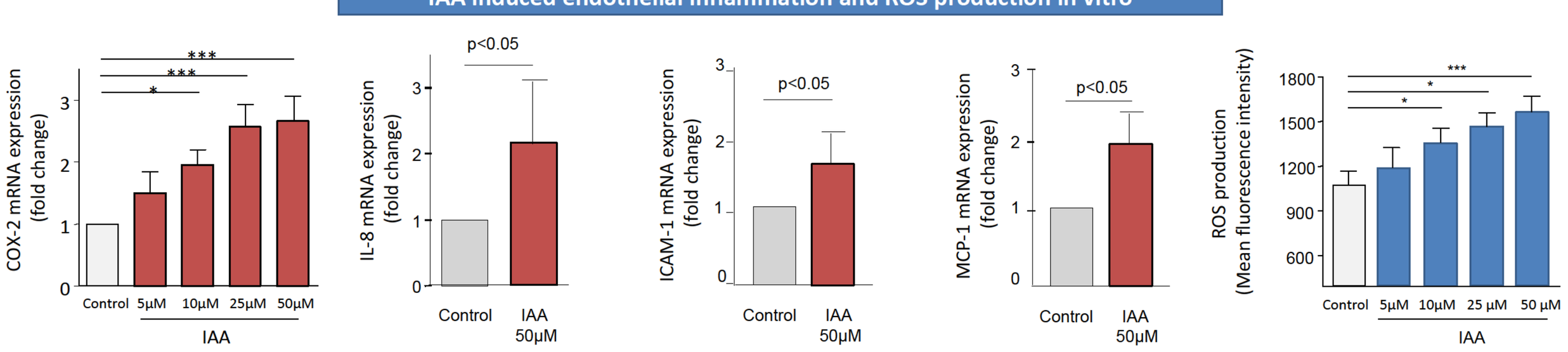
Major cardiovascular event (event 35/120)	RR	95% CI	P
Unadjusted	2.16	1.26 to 3.71	0.005
Model 1 [a]	1.81	1.04 to 3.14	0.037
Model 2 [b]	1.91	1.10 to 3.32	0.023
Model 3 [c]	1.89	1.08 to 3.33	0.027
Model 4 [d]	1.77	1.02 to 3.09	0.043
Model 5 [e]	1.39	0.77 to 2.48	0.270

[a] adjusted for demographics
[b] adjusted for framingham cardiovascular risk factors (cholesterol, systolic blood pressure, smoking)
[c] adjusted for factors associated with mortality in CKD (CRP, phosphate, BMI, albumin)
[d] adjusted for factors associated with mortality in univariate analysis (diastolic blood pressure, history of CVD)
[e] adjusted for CKD stage

IN VITRO STUDY

Endothelial cells were treated with IAA during 4 or 24 hours. Inflammation was demonstrated by increased mRNA expression of inflammatory molecules COX-2, IL-8, ICAM-1, MCP-1, studied by RT-qPCR. Intracellular ROS production was detected by measuring the fluorescence of 6-carboxy-H2DCF-DA-di-AM.

IAA induced endothelial inflammation and ROS production in vitro



CONCLUSION

Serum IAA is a significant predictor for mortality and cardiovascular event in CKD patients. IAA could be involved in cardiovascular disease associated with CKD by inducing endothelial inflammation and oxidative stress.

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