ELEVATED PLASMA CYCLOPHILIN A IN HEMODIALYSIS AND PERITONEAL DIALYSIS PATIENTS: A NOVEL LINK TO SYSTEMIC INFLAMMATION AND CARDIOVASCULAR DISEASE

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BACKGROUND

Cyclophilin A (CyPA) has emerged as a novel mediator of oxidative stress and inflammation and a major player in cardiovascular disease, diabetes, viral infections, and neurodegenerative and thrombotic disorders. CyPA is an abundant intra-cellular protein which is released by certain cell types spontaneously or in response to inflammatory mediators, hypoxia, oxidative stress and hyperglycemia. Many of these conditions are either present or frequently occur in ESRD patients and can thus stimulate release of CyPA thereby amplifying systemic inflammation. To our knowledge, the effect of ESRD and dialysis modalities on circulating CyPA has not been previously investigated. This study tested the hypothesis that extracellular CyPA is elevated in ESRD patients maintained on hemodialysis and peritoneal dialysis.

METHOD

CyPA, hsCRP, and lipid levels were measured in the fasting plasma samples from 20 hemodialysis and 20 peritoneal dialysis patients, and 20 healthy age- and gender-matched controls. Left ventricular (LV) mass, LV end-systolic and end-diastolic volumes, ejection fraction and and pulse wave velocity and ankle-brachial index were determined.

RESULTS

Plasma CyPA concentration in the hemodialysis (105.3 ± 6.2 ng/ml) and PD (106.8 ± 9.0 ng/ml) groups were significantly higher than that in the control group (29.7 ± 4.1 ng/ml). This was associated with significant elevation of hsCRP, IL-6, TNF-α, plasma atherogenic index [log(triglyceride/HDL-cholesterol)], systolic and diastolic blood pressure, LV mass, LV end-diastolic and end- systolic volumes, and pulse wave velocity coupled with significant reduction in LV ejection fraction and ankle-brachial index. Plasma CyPA concentration showed direct correlation with hsCRP, IL-6, TNF-α, plasma atherogenic index, pulse wave velocity, systolic and diastolic blood pressure and inverse correlation with ankle-brachial index and HDL-cholesterol concentration.

Fig. 1. **Box plots depicting plasma cyclophilin A concentrations in the control, hemodialysis and peritoneal dialysis group**

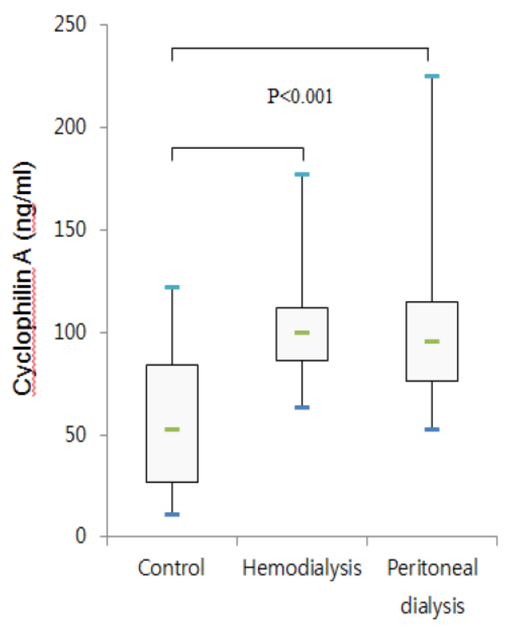

Table 1. General data on hemodialysis, peritoneal dialysis, and healthy control groups

	Control	Hemodialysis	Peritoneal dialysis
Age (y)	47.7 ± 8.5	49.4 ± 11.8	50.1 ± 8.4
Female sex (%)	10 (50)	10 (50)	10 (50)
Systolic blood pressure (mmHg)	118.9 ± 7.2	140.7 ± 17.8[a]	138.5 ± 26.4[a]
Diastolic blood pressure (mmHg)	76.8 ± 8.1	85.5 ± 15.1[a]	84.0 ± 13.1[a]
Body mass index (kg/m^2)	23.3 ± 3.4	24.2 ± 3.8	25.1 ± 3.1
Hemoglobin (g/dl)	14.2 ± 1.6	10.1 ± 0.8[a]	10.2 ± 1.1
Serum albumin (g/dl)	4.5 ± 0.2	3.6 ± 0.3[a]	3.2 ± 0.5[a,d]
Calcium (mmol/l)	9.5 ±0.4	8.3 ± 0.5[b]	8.2 ± 0.7[a]
Phosphorus (mmol/l)	3,5 ± 0.8	5.9 ± 2.2[a]	5.4 ± 1.9[a]
Ca X P (mg^2/dl^2)	33.2 ± 8.6	48.5 ± 17.3[a]	44.2 ± 15.3[a]
Serum urea nitrogen (mg/dl)	11.5 ± 2.8	76.9 ± 29.0[a]	57.2 ± 16.2[a]
Serum creatinine (mg/dl)	0.9 ± 0.2	10.6 ± 2.6[a]	10.6 ± 4.6[a]
hs-CRP (mg/dl)	0.03 ± 0.01	0.29 ± 0.29[a]	0.24 ± 0.24[a]
Total cholesterol (mg/dl)	178.4 ± 34.1	153.1 ± 31.3[b]	212.3 ± 30.8[a,d]
LDL cholesterol (mg/dl)	85.1 ± 27.4	88.3 ± 24.5[b]	135.8 ± 19.9[a,d]
HDL cholesterol (mg/dl)	54.3 ± 111.1	40.1 ± 9.9[b]	36.6 ± 8.9[a]
Triglyceride (mg/dl)	93.5 ± 45.6	113.5 ± 64.5	194.0 ± 97.6[a,c]
Atherogenic index of plasma	0.19 ± 0.06	0.43 ± 0.08[a]	0.64 ± 0.07[a,d]
Body mass index (kg/m^2)	22.3 ± 3.4	24.2 ± 3.8	25.1 ± 3.1
CK-MB (ng/ml)	1.7 ± 0.4	2.4 ± 1.7	2.9 ± 2.4
cTnI (ng/ml)	0.02 ± 0.01	0.03 ± 0.03	0.05 ± 0.09
Uric acid (mg/dl)	4.2 ± 1.2	7.4 ± 1.5[a]	7.3 ± 1.5[a]
Cyclophillin A (ng/ml)	57.5 ± 17.8	104.5 ± 19.5[a]	106.2 ± 35.2[a]

Table 2. Plasma cyclophilin A, hs-CRP, IL-6, and TNF-α concentrations in hemodilaysis, peritoneal dialysis and healthy control group

	Control (n=20)	Hemodialysis (n=20)	Peritoneal dialysis (n=20)
Cyclophillin A (ng/ml)	29.7 ± 4.1	105.3 ± 6.2[a]	106.8 ± 9.0[a]
hs-CRP (mg/dl)	0.03 ± 0.01	0.29 ± 0.29[a]	0.24 ± 0.24[a]
IL-6 (pg/ml)	1.3 ± 0.2	5.2 ± 0.4[a]	5.2 ± 0.5[a]
TNF-α (pg/ml)	1.4 ± 0.1	4.6 ± 0.2[a]	4.8 ± 0.3[a]

a= P < 0.01 versus control group; b= P < 0.05 versus control group; c =P < 0.01 versus hemodialysis group; d= P < 0.05 versus hemodialysis group.

CONCLUSION

Plasma CyPA concentration is markedly elevated and positively correlates with the markers of systemic inflammation and cardiovascular disease in hemodialysis and peritoneal dialysis patients.

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