Elevated Plasma Cyclophillin A in Hemodialysis and Peritoneal Dialysis Patients

A Novel Link to Systemic Inflammation

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Introduction. Cyclophillin A has emerged as a novel mediator of oxidative stress and inflammation and a major player in cardiovascular disease, diabetes mellitus, viral infections, and neurodegenerative and thrombotic disorders. Cyclophillin A 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 patients with end-stage renal disease and can stimulate release of cyclophillin A, thereby amplifying systemic inflammation. To our knowledge, the effect of end-stage renal disease and dialysis modalities on circulating cyclophillin A has not been previously investigated. This study tested the hypothesis that extracellular cyclophillin A is elevated in patients maintained on hemodialysis and peritoneal dialysis.

Materials and Methods. Cyclophillin A, high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α, and lipid levels were measured in the fasting plasma samples from 20 hemodialysis and 20 peritoneal dialysis patients, and 20 age- and sex-matched controls.

Results. Plasma cyclophillin A concentration in the patients on hemodialysis (105.3 ± 6.2 ng/mL) and peritoneal dialysis (106.8 ± 9.0 ng/mL) were significantly higher than that in the control group (29.7 ± 4.1 ng/mL). This was associated with significant elevation of high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α. Plasma cyclophillin A concentration showed direct correlations with high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α, and an inverse correlation with high-density lipoprotein cholesterol concentration.

Conclusions. Plasma cyclophillin A concentration is markedly elevated and positively correlates with the markers of systemic inflammation in hemodialysis and peritoneal dialysis patients.

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INTRODUCTION

Systemic oxidative stress and inflammation are invariably present and play a central part in the pathogenesis of cardiovascular disease, cachexia, anemia, and various other complications in patients with end-stage renal disease (ESRD).[1-6] Several factors contribute to the ESRD-associated systemic inflammation and oxidative stress including uremic toxins and metabolites, hypervolemia, hypertension, upregulation and activation of tissue angiotensin system, impaired nuclear factor (erythroid-derived 2)-like 2-mediated expression of endogenous

antioxidant and detoxifying molecules,[7-10] disruption of intestinal epithelial barrier structure and function leading to endotoxemia,[11-14] and altered gut microbial flora[15,16,18] among others.

Cyclophillin A has emerged as a novel mediator of oxidative stress and inflammation and a major player in cardiovascular disease, diabetes mellitus, viral infections, neurodegenerative diseases, and thrombotic disorders.[19,20] Cyclophillin A is an abundant intracellular housekeeping protein, which belongs to the cyclophillin family of proteins found in all mammalian cells.[20] Although cyclophillin A is an intracellular protein, a variety of cell types release cyclophillin A spontaneously or in response to inflammatory mediators, hypoxia, oxidative stress, and other stimuli. For instance, macrophages release cyclophillin A following exposure to endotoxin or high glucose concentrations and during their transformation to foam cell[21-23]; cardiomyocytes release cyclophillin A when exposed to hypoxia[24]; and platelets release cyclophillin A upon activation.[25] Release of cyclophillin A to the extracellular space requires its acetylation, which amplifies its pro-inflammatory property.[26] In addition cell death results in the release of cyclophillin A. The extracellular cyclophillin A binds to the extracellular matrix metalloproteinase inducer (CD147), which is widely expressed on cardiovascular cell types.[27] The cyclophillin A-CD147 complex is a powerful chemotactic factor for T cells, monocytes, and neutrophilic and eosinophilic polymorphonuclear leukocytes and promotes activation of nuclear factor kappa-light-chain-enhancer of activated B cells, phosphoinositide 3-kinase, or extracellular signal-regulated kinase in relevant cell types,[28,29] as well as activation of extracellular matrix metalloproteinases.[23,30] There is mounting evidence supporting the role of cyclophillin A-CD147 interaction in endothelial injury and dysfunction,[31,32] vascular remodeling,[33] atherosclerosis,[19,23,25,34] vascular thrombosis,[35] myocardial infarction,[36] and cardiomyopathies.[37,38] In addition, cyclophillin A plays a critical role in replication and release of hepatitis B and C viruses.[39-42]

Many of the conditions known to promote release of extracellular cyclophillin A, ie, oxidative stress, inflammation, hyperglycemia, and ischemia or hypoxia are either present or frequently occur in ESRD patients. As noted above, oxidative stress and inflammation are commonly present and are frequently accompanied by endotoxemia in patients with ESRD.[43,44] In addition, due to diabetes mellitus, which is the most common cause of ESRD and peritoneal dialysis (PD) procedure with high glucose dialysis solutions, ESRD patients frequently experience episodes of hyperglycemia. Moreover, intradialytic and postdialysis hypotension commonly result in episodes of tissue ischemia and fluid overload, and anemia and dialysis-induced hypoventilation result in hypoxia and impaired oxygen delivery. Together, these conditions can stimulate release and increase plasma concentration of cyclophillin A, which can amplify systemic inflammation and create a vicious circuit. To our knowledge, the effect of ESRD and dialysis modalities on circulating cyclophillin A has not been previously investigated. The present study was undertaken to test the hypothesis that extracellular cyclophillin A is elevated in ESRD patients maintained on hemodialysis and PD.

MATERIALSANDMETHODS

Study Groups

Twenty hemodialysis patients (10 men and 10 women; mean age, 49.4 ± 11.8 years), and 20 PD patients (10 men and 10 women; mean age, 50.1 ± 8.4 years) were recruited into the study. The underlying causes of kidney disease in the hemodialysis group included diabetes mellitus in 10, hypertension in 8, and chronic glomerulonephritis in 2 patients. The underlying causes of kidney disease in the PD group were diabetes mellitus in 12, hypertension in 5, and chronic glomerulonephritis in 3 patients. Duration of dialysis in the hemodialysis group (24.9 ± 14.3 months) was comparable to that of the PD group (21.6 ± 11.3 months). Twenty age- and sex-matched healthy individuals (10 men and 10 women; mean age, 47.7 ± 8.5 years) served as controls.

Individuals younger than 18 years, those with a history of malignancy or chronic liver disease, and those with a history of infection within the previous 4 weeks were excluded from the study. The study protocol was approved by the Human Subjects Institutional Review Board of the Inje University Haeundae Paik Hospital (129792-2014-045), and all participants signed the informed consent forms.

Laboratory Measurements

Fasting blood samples were obtained by

venipuncture from all patients and controls. Total cholesterol, low-sensity lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol, triglyceride, creatinine, and urea nitrogen were measured by the central laboratory of the Inje University Haeundae Paik Hospital.

Plasma cyclophillin A was measured by an enzyme-linked immunosorbent assay using the kit purchased from Cusabio Biotech (Carlsbad, CA, USA) according to the manufacturer's specifications. High-sensitivity C reactive protein (HSCRP) was measured as a biomarker of systemic inflammation by turbidimetric immunoassay using the kit purchased from Sekisui Chemical (Osaka, Japan) according to the manufacturer's specifications. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured by and enzyme-linked immunosorbent assay using the kit purchased from R&D Systems (Minneapolis, MN, USA).

Statistical Analysis

The analysis of variance and a regression model were used in statistical analysis of the data. Continuous variable were expressed as mean ± standard error of the mean. *P* values less than .05 were considered significant.

RESULTS

Characteristics of Study Groups

Data are shown in Table 1. Arterial blood pressure in hemodialysis and PD groups were comparable and significantly higher than that found in the control group. Blood hemoglobin concentrations in the hemodialysis and PD groups were comparable and significantly lower than that found in the control group. Serum albumin concentration in the PD group was significantly lower than in the hemodialysis group and significantly lower in both than in the controls. Serum calcium was significantly lower whereas serum phosphorus and calcium-phosphorus product were significantly higher in the hemodialysis and PD groups compared with the corresponding values found in the control group. Serum urea nitrogen and creatinine levels were markedly elevated and serum uric acid was modestly increased in the hemodialysis and PD groups as compared to the corresponding values found in the control group. Serum total cholesterol, LDLC, and triglyceride concentrations were significantly higher in the PD group than in the hemodialysis and control groups. Serum high-density lipoprotein cholesterol was significantly lower in both hemodialysis and PD groups than in the control group.

Plasma Cyclophillin A and Inflammatory Markers

The laboratory results are shown in Table 2. Plasma cyclophillin A concentration in the hemodialysis and peritonial dialysis groups were significantly higher than that in the control group ($P < .001$). This was associated with significant elevation

Table 1. Laboratory and Clinical Measures in Hemodialysis, Peritoneal Dialysis, and Control Groups

Parameter	Control Group (n = 20)	Hemodialysis Group (n = 20)	Peritoneal Dialysis Group (n = 20)
Systolic blood pressure, mmHg	118.9 ± 7.2	140.7 ± 17.8*	138.5 ± 26.4*
Diastolic blood pressure, mmHg	76.8 ± 8.1	85.5 ± 15.1*	84.0 ± 13.1*
Hemoglobin, g/dL	14.2 ± 1.6	10.1 ± 0.8*	10.2 ± 1.1
Serum albumin, g/dL	4.5 ± 0.2	3.6 ± 0.3*	3.2 ± 0.5*§
Calcium, mmol/L	9.5 ± 0.4	8.3 ± 0.5†	8.2 ± 0.7*
Phosphorus, mmol/L	35 ± 0.8	5.9 ± 2.2*	5.4 ± 1.9*
Calcium-phosphorus product, mg^2/dL^2	33.2 ± 8.6	48.5 ± 17.3*	44.2 ± 15.3*
Serum urea nitrogen, mg/dL	11.5 ± 2.8	76.9 ± 29.0*	57.2 ± 16.2*
Serum creatinine, mg/dL	0.9 ± 0.2	10.6 ± 2.6*	10.6 ± 4.6*
Total cholesterol, mg/dL	178.4 ± 34.1	153.1 ± 31.3†	212.3 ± 30.8*§
Low-density lipoprotein cholesterol, mg/dL	85.1 ± 27.4	88.3 ± 24.5†	135.8 ± 19.9*§
High-density lipoprotein cholesterol, mg/dL	54.3 ± 111.1	40.1 ± 9.9†	36.6 ± 8.9*
Triglyceride, mg/dL	93.5 ± 45.6	113.5 ± 64.5	194.0 ± 97.6*‡
Uric acid, mg/dL	4.2 ± 1.2	7.4 ± 1.5*	7.3 ± 1.5*

*$P < 0.01$ versus the control group
†$P < 0.05$ versus the control group
‡$P < 0.01$ versus the hemodialysis group
§$P < 0.05$ versus the hemodialysis group

Table 2. Plasma Cyclophillin A, High-sensitivity C-Reactive Protein, Interleukin-6, and Tumor Necrosis Factor-α Concentrations in Hemodialysis, Peritoneal Dialysis and Control Groups

Parameter	Control Group (n = 20)	Hemodialysis Group (n = 20)	Peritoneal Dialysis Group (n = 20)
Cyclophillin A, ng/mL	29.7 ± 4.1	105.3 ± 6.2*	106.8 ± 9.0*
High-sensitivity C-reactive protein, mg/dL	0.03 ± 0.01	0.29 ± 0.29*	0.24 ± 0.24*
Interleukin-6, pg/mL	1.3 ± 0.2	5.2 ± 0.4*	5.2 ± 0.5*
Tumor necrosis factor-α, pg/mL	1.4 ± 0.1	4.6 ± 0.2*	4.8 ± 0.3*

*P < 0.01 versus the control group

of plasma HSCRP, IL-6, and TNF-α. There was a significant direct correlation between plasma cyclophillin A and HSCRP (r = 0.436, P = .01), IL-6 (r = 0.526, P = .001), TNF-α (r = 0.651, P = .001), systolic blood pressure (r = 0.386, P = .01), and diastolic blood pressure (r = 0.360, P = 0.05), and an inverse relationship between cyclophillin A and plasma high-density lipoprotein cholesterol concentration (r = -0.634, P = 0.01) in the study population.

DISCUSSION

The present study revealed a marked elevation of plasma cyclophillin A levels in stable patients with ESRD maintained on hemodialysis and PD modalities. Plasma cyclophillin A concentration showed a direct correlation with HSCRP, IL-6, and TNF-α, the well-known markers of systemic inflammation. This finding is consistent with participation of cyclophillin A and systemic inflammation in a vicious circuit wherein inflammation promotes release of cyclophillin A and cyclophillin A amplifies the inciting inflammation.

As noted in the introduction, emerging data have demonstrated the role of cyclophillin A in the pathogenesis of atherosclerosis, arteriosclerosis, and cardiovascular disease,[19,37,47] which are the main causes of morbidity and mortality in chronic kidney disease (CKD) population. The role of cyclophillin A in the pathogenesis of arteriosclerosis and arterial remodeling has been demonstrated in several studies conducted in experimental animals. Using carotid artery ligation model, Satoh and coworkers found significant protection against intimal and medial hyperplasia in genetically cyclophillin A deficient compared to the wild type mice.[33] This was associated with diminished vascular smooth muscle cell proliferation and reduced monocyte infiltration, which are critical steps in arteriosclerosis and atherosclerosis. Likewise, cyclophillin A-deficient mice have been shown to be completely protected against angiotensin-2 induced abdominal aortic aneurysm.[46] This phenomenon is attributed to attenuation of tissue inflammation and oxidative stress and suppression of metalloproteinases, which are essential for aneurysm formation.

Compared with the hemodialysis group, the PD patients exhibited significant increase in serum total and LDLC and triglyceride concentrations. This phenomenon is caused by significant daily losses of protein in the effluent peritoneal dialysis fluid which simulate nephrotic syndrome in these functionally anephric patients.[47,48]

Cyclophillin A has a peptidylprolyl-cis/trans isomerase enzymatic activity which regulates intracellular folding and trafficking of proteins. Cyclophillin A was first identified in 1984 to be the intracellular protein which binds the immunosuppressive drug, cyclosporine A. Cyclophillin A was shown to bind cyclosporine A and form a complex that can suppress immune response by blocking calcineurin-dependent activation of nuclear factor activating T lymphocytes.[49] Due to its potent immunosuppressive property and other side effects cyclosporine A is not suitable for the treatment of systemic inflammation in patients with CKD, type-2 diabetes mellitus, atherosclerosis, and other chronic illnesses. Presently, drugs that can exclusively block extracellular cyclophillin A and lack immunosuppressive properties are not available. Development of such agents will undoubtedly prove highly effective in the management of chronic inflammatory diseases including CKD.

Due to occasional blood transfusion and surgical procedures, patients with advanced CKD are at a high risk of exposure to viral hepatitis. Given the central role of cyclophillin A in proliferation and release of hepatitis B and C viruses,[39-42] elevation of cyclophillin A level in hemodialysis and peritoneal

dialysis patients shown here may impact the course and outcomes of these infections.

Given the role of extracellular cyclophillin A as a biomarker and potent mediator of oxidative stress, inflammation, and cardiovascular disease, which are the common features of CKD, cyclophillin A is an attractive diagnostic and therapeutic target in CKD population.

The authors wish to acknowledge the limitations of the study including the relatively small size of the enrolled populations and cross-sectional nature of the study. Longitudinal studies enrolling larger number of participants are needed to confirm the results of the present study and to determine the impact of elevated cyclophillin A on morbidity and mortality in CKD populations.

CONCLUSIONS

Plasma cyclophillin A 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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CONFLICT OF INTEREST

None declared.

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