

Endotoxemia is Related to Systemic Inflammation and Atherosclerosis in Peritoneal Dialysis Patients

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Background and objectives: Systemic inflammatory state is a hallmark of peritoneal dialysis (PD) patients, but its etiology remains obscure. Because circulating microbial products are an important cause of systemic immune activation in other conditions such as HIV infection, it was hypothesized that endotoxemia is a cause of systemic inflammatory state and atherosclerosis in PD patients.

Design, setting, participants, & measurements: Plasma lipopolysaccharide (LPS) levels in 30 consecutive new PD patients were measured. The result was compared with serum C-reactive protein (CRP) level, peritoneal transport status, history of pre-existing cardiovascular diseases, and carotid intima media thickness (IMT) by Doppler ultrasound.

Results: Among the 30 PD patients, there were 17 men. The average age was 53.7 ± 15.1 yr. The average endotoxin concentration of PD patients was 0.44 ± 0.18 EU/ml, which was significantly higher than that of patients with chronic kidney disease secondary to Ig-A nephropathy (IgAN) (0.035 ± 0.009 EU/ml, $P < 0.0001$) and the controls (0.013 ± 0.007 EU/ml, $P < 0.0001$). In PD patients, plasma LPS concentration had a significant correlation with serum CRP ($r = 0.415$, $P = 0.025$) and serum albumin level ($r = -0.394$, $P = 0.034$). In contrast, plasma LPS level did not correlate with Charlson's Comorbidity Index, peritoneal transport characteristics, or nutritional indices. Patients with pre-existing cardiovascular disease (CVD) had higher plasma LPS level than those without CVD (0.53 ± 0.19 versus 0.36 ± 0.16 EU/ml, $P = 0.016$). Plasma LPS level correlated with carotid IMT ($r = 0.438$, $P = 0.016$).

Conclusions: It was found that endotoxemia was probably common in PD patients, and the degree of circulating endotoxemia might be related to the severity of systemic inflammation and features of atherosclerosis. This result suggests that endotoxemia may have a contributory role to the systemic inflammatory state and accelerated atherosclerosis in PD patients.

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Patients with chronic kidney disease (CKD) are at high risk of developing CVD (1,2). Longitudinal studies have established that CVD events occur more frequently than renal events in CKD, and CVD mortality rates are in fact higher than the rates of reaching ESRD (3). CVD shares many similar risk factors with CKD, such as diabetes and hypertension (4). However, after accounting for traditional risk factors, CKD remains an independent risk factor for CVD (5). It is now recognized that systemic inflammation plays a key role in atherosclerosis (6) and is an important contributor to CVD morbidity and mortality in CKD patients (7).

Around 30 to 50% of CKD or dialysis patients have serologic evidence of an activated inflammatory response (8-10). The mechanisms of systemic inflammation in CKD is complicated and include decreased renal clearance of pro-inflammatory cytokines, comorbidity (e.g. autoimmune disease),

accumulation of advanced glycation end-products, persistent infections, and patient-specific processes such as clotted access grafts (7). However, the principal underlying causes of immune activation in CKD remains elusive. It is long postulated that there exists an infectious risk factor of atherogenesis and CVD, but the nature of such process remains obscure. It is now recognized that endotoxemia constitutes a strong risk factor of early atherogenesis in subjects with chronic or recurrent bacterial infections (11). Epidemiologic studies show that even a low-level endotoxemia constitutes a strong risk factor for the development of atherosclerosis (12). Circulating LPS is bioactive *in vivo* and correlates with measures of innate and adaptive immune activation (13), and an epidemiologic study suggests that the atherogenic potential of endotoxemia is affected by concomitant immune activation (14). It is recently shown that circulating microbial products, probably derived from the gastrointestinal tract (15), are a cause of HIV-related systemic immune activation. A recent study (16) shows that infusion of LPS led to a significant decrease in peripheral endothelial progenitor cells, which represents a strong predictor of CVD (17).

There is also early evidence that circulating microbial products, probably derived from the gastrointestinal tract, are not

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uncommon in CKD patients. The intestinal mucosa barrier is impaired and bacterial translocation occurs in experimental uremia (18). Translocation of bowel flora is a cause of gram-negative peritonitis in PD patients (19). We hypothesize that circulating microbial products contribute to the persistent inflammatory state and represents a reversible CVD risk factor in PD patients.

Patients and Methods

Patient selection

The Clinical Research Ethical Committee of the Chinese University of Hong Kong approved this study. We studied 30 new PD patients. These were subjects with CKD who participated in a previous study of our group (20) on the relation between carotid IMT, inflammation, and premature atherosclerosis. They progressed to dialysis-dependent renal failure and were put on PD. A blood test for circulating LPS level and a standard peritoneal permeability test (PET) (21) were performed within 2 mo after the commencement of PD, when the patient was in a euvolemic state. On the day before PET, 24-h urine and dialysate collection was performed for assessment of nutritional status. The presence of diabetes and a history of CVD at initiation of dialysis were recorded. Pre-existing CVD was defined as angina, class III to IV congestive heart failure, a history of previous myocardial infarction, cerebrovascular accident, or amputation for vascular disease. The modified Charlson's Comorbidity Index was used to calculate a comorbidity score (22). We further studied the circulating LPS level of ten patients with mild-to-moderate CKD secondary to IgAN, with average serum creatinine levels of 1.71 ± 1.32 mg/dl (151.3 ± 116.3 μ mol/L), and six healthy subjects as control.

Circulating LPS level

The method of plasma LPS quantification has been described previously (15). Briefly, plasma samples were diluted to 20% with endotoxin-free water and then heated to 70°C for 10 min to inactivate plasma proteins. We then quantified plasma LPS with a commercially available Limulus Amebocyte assay (Cambrex, Verviers, Belgium) according to the manufacturer's protocol. The detection limit of this assay was 0.01 EU/ml. Samples with LPS level below the detection limit were taken as 0 EU/ml. All samples were run in duplicate and background subtracted.

Study of Peritoneal Transport

PET was performed by the method of Twardowski (21). Briefly, a 4-h dwell study was carried out with 2 L of dextrose 2.5% dialysis fluid (Dianeal, Baxter-Travenol, Deerfield, IL). Dialysate creatinine and glucose levels at 0, 2, and 4 h, and plasma creatinine and glucose levels at 2 h were measured. Drainage and ultrafiltration volumes at 4 h were documented. Dialysate-to-plasma ratios of creatinine (D/P) at 0, 2, and 4 h were calculated after correction of glucose interference. Mass transfer area coefficients of creatinine normalized for body surface area were calculated by the formula described by Krediet (23). Body surface area was determined from body weight and height by nomogram (24).

Peritoneal Protein and Albumin Excretion Rate

During the PET, dialysate albumin and total protein concentrations at 4 h were determined by a fully automated analyzer (Konelab 60, Thermo Clinical LabSystems) as described previously (25), and the concentrations were adjusted for the dialysate creatinine concentration. In all measurements, creatinine concentration in dialysate was cor-

rected for glucose interference according to a formula provided by our laboratory (26).

Dialysis Adequacy, Nutrition, and Inflammation Markers

On the day before PET, 24 h-urine and dialysate collection was performed to calculate total Kt/V. Normalized protein nitrogen appearance was calculated by the modified Bergstrom's formula (27). Serum CRP was measured by the Tina-quant CRP (Latex) ultrasensitive assay (Roche Diagnostics GmbH, Mannheim, Germany).

B-mode Carotid Doppler Examination

As described in our previous study (20,25), Doppler ultrasonographic examinations were performed using an ATL HDI 5000 ultrasound scanner (Bothell, WA). A trained sonographer scanned the right and left common carotid arteries, the carotid bulbs, and the first 2 cm of the internal and external carotid arteries. For each location, the sonographer visualized the vessel in multiple planes and then focused on the interfaces required to measure IMT as well as any areas of calcified or ulcerated plaque. Carotid plaques were defined as echogenic structures showing protrusion into the lumen with focal widening that was 50% greater than the IMT of adjacent sites. All measurements were performed by technicians who were blinded to the clinical details and laboratory results of the patients.

Statistical Analyses

Statistical analyses were performed by SPSS for Windows software version 11.0 (SPSS Inc., Chicago, IL). Results were expressed as mean \pm SD unless otherwise specified. Comparisons between groups were performed by χ^2 test or Mann-Whitney U test as appropriate. Correlation between continuous variables was examined by Spearman's rank correlation coefficient. Factors independently associated with plasma LPS level were further explored by a multiple linear regression model with backwards-stepwise analysis. A *P* value of less than 0.05 was considered significant. All probabilities were two-tailed.

Results

We studied a total of 30 patients. The demographic and baseline clinical data are summarized in Table 1. The average endotoxin concentration of PD patients was 0.44 ± 0.18 EU/ml, which was significantly higher than that of patients with CKD secondary to IgAN (0.035 ± 0.009 EU/ml, *P* < 0.0001) and the controls (0.013 ± 0.007 EU/ml, *P* < 0.0001) (Figure 1).

Plasma LPS and Inflammation

Plasma LPS level was not affected by diabetic status, average blood pressure, fasting total cholesterol, LDL cholesterol, or total triglyceride level (details not shown). There was, however, a significant correlation between plasma LPS level and serum CRP (*r* = 0.415, *P* = 0.025) and serum albumin level (*r* = -0.394, *P* = 0.034) (Figure 2). In contrast, plasma LPS level did not correlate with peritoneal transport characteristics, as represented by mass transfer area coefficients creatinine (*r* = 0.194, *P* = 0.3), or peritoneal permeability to albumin (*r* = 0.058, *P* = 0.8). Plasma LPS level did not correlate with total Kt/V (*r* = 0.133, *P* = 0.5), residual GFR (*r* = 0.001, *P* = 1.0), or normalized protein nitrogen appearance (*r* = 0.219, *P* = 0.25).

Table 1. Demographics and clinical information

Number of Patients	30
Sex (men:women)	17:13
Age (yr)	53.7 ± 15.1
Body height (cm)	161.4 ± 10.2
Body weight (kg)	60.2 ± 11.2
Renal diagnosis, number of cases (%)	
GN	16 (53.3%)
diabetic nephropathy	9 (30.0%)
polycystic kidney	1 (3.3%)
obstructive uropathy	1 (3.3%)
others/unknown	3 (10%)
Major comorbidity, number of cases (%)	
diabetes	11 (36.7%)
cardiovascular disease	12 (40.0%)
Charlson's comorbidity index	5.0 ± 2.6
Fasting lipid profile (mmol/l)	
total cholesterol	5.04 ± 0.93
LDL cholesterol	2.87 ± 0.99
total triglyceride	1.66 ± 0.96
Serum C-reactive protein (mg/dl)	2.71 ± 2.31

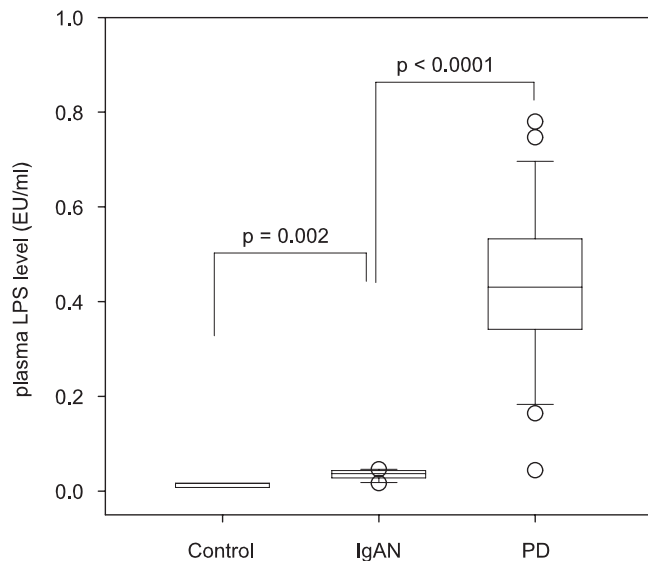


Figure 1. Comparison of plasma lipopolysaccharide (LPS) level between patients on peritoneal dialysis (PD), chronic kidney disease secondary to Ig-A nephropathy (IgAN) and controls. The boxes indicate median, 25th, and 75th percentile; whisker caps indicate 5th and 95th percentile; open circles indicate outliers. (Overall Kruskal-Wallis test, $P < 0.0001$.)

Plasma LPS and Atherosclerosis

Twelve patients had pre-existing CVD at the initiation of dialysis. They had higher plasma LPS levels than those without CVD (0.53 ± 0.19 versus 0.36 ± 0.16 EU/ml, $P = 0.016$). There was a significant correlation between plasma LPS level and carotid IMT ($r = 0.438$, $P = 0.016$) (Figure 3). By carotid ultrasound, 11 patients had significant carotid plaques. These patients also had higher plasma LPS levels than those without

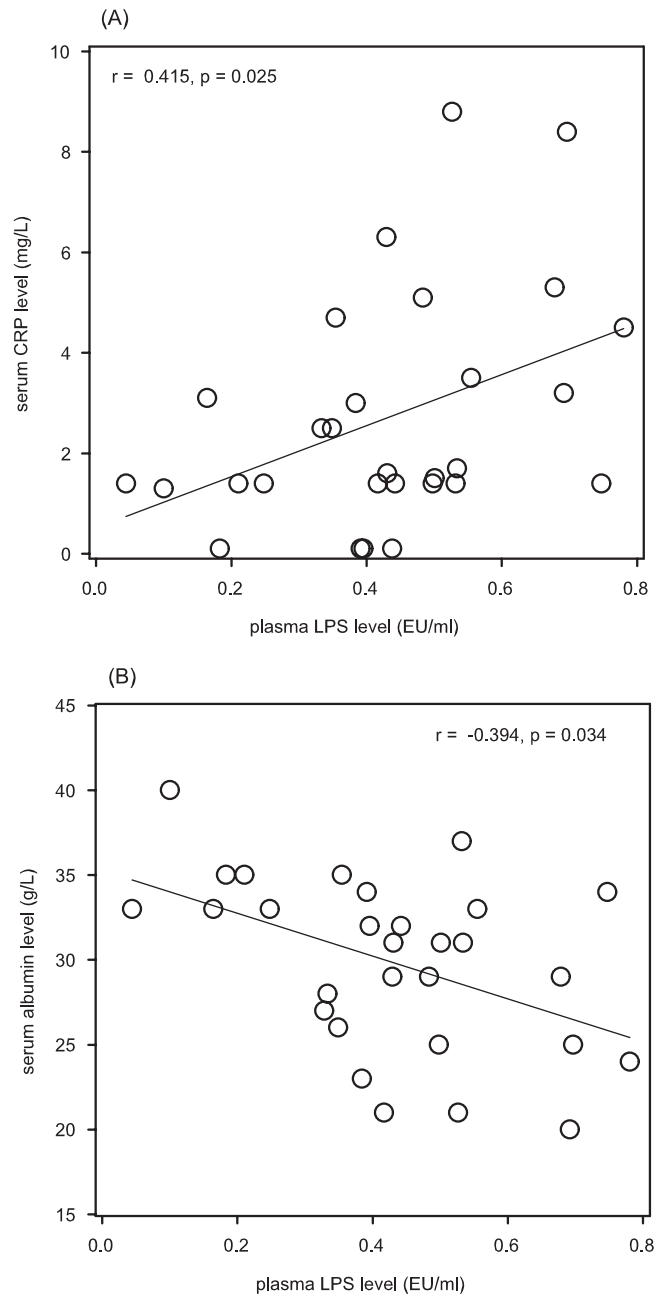


Figure 2. Relation between plasma LPS level and (A) serum C-reactive protein (CRP), and (B) serum albumin level.

carotid plaque (0.55 ± 0.16 versus 0.36 ± 0.16 EU/ml, $P = 0.005$).

In total, 13 patients had neither pre-existing CVD nor carotid plaque from Doppler study. These patients had significantly lower plasma LPS levels than those with either (0.32 ± 0.17 versus 0.51 ± 0.16 EU/ml, $P = 0.005$) (Figure 4). Multiple linear regression analysis showed that carotid IMT and serum albumin level were the only independent factors associated with plasma LPS level (Table 2).

Discussion

In this study we found that endotoxemia was common in PD patients, and the degree of circulating endotoxemia was related

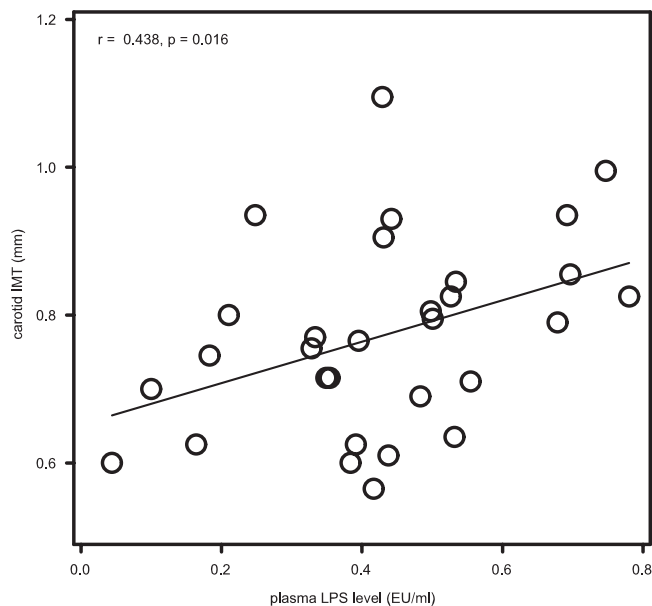


Figure 3. Relation between plasma LPS level and intima-media thickness (IMT) of carotid artery as determined by Doppler ultrasound.

to the severity of systemic inflammation and features of atherosclerosis. The correlation between endotoxemia and atherosclerosis was notably unrelated to other traditional cardiovascular risk factors.

The phenomenon of circulating endotoxemia in renal failure subjects has not been systemically studied previously. Our

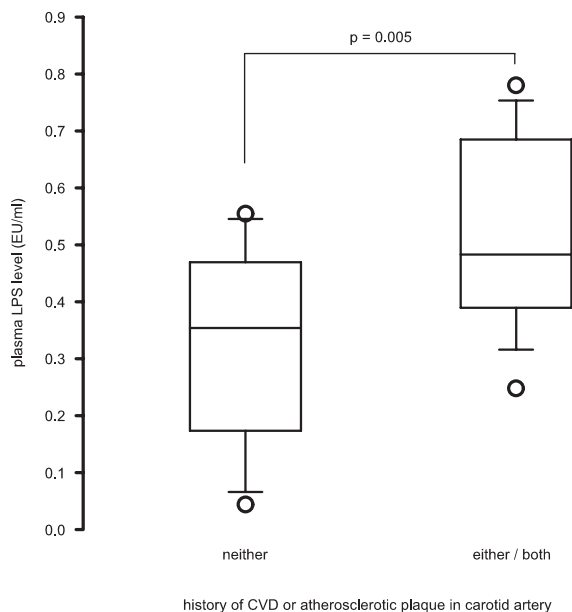


Figure 4. Comparison of plasma LPS level between patients with neither a history of cardiovascular disease (CVD) nor atherosclerotic plaque identified by carotid Doppler ultrasound and patients with either or both problems. The boxes indicate median, 25th, and 75th percentile; whisker caps indicate 5th and 95th percentile; open circles indicate outliers.

Table 2. Summary of multiple linear regression model on factors associated with plasma lipopolysaccharide level

Variable	B coefficient	95% Confidence Interval	P value
Carotid IMT	0.534	0.060 to 1.026	0.029
Serum albumin	-0.016	-0.004 to -0.029	0.01
Model constant	0.500	-0.050 to 1.051	0.073

observation agrees with the previous study of Kiechl *et al.* (11) in subjects with recurrent infection and early atherosclerosis, as well as the study of Wiedermann *et al.* (12) in a general population with atherosclerosis. This latter study showed that subjects with circulating LPS levels beyond 50 pg/ml (90th percentile of normal population) faced a threefold risk of incident atherosclerosis. In the study presented here, 24 of the 30 PD patients (80%) had such a high circulating LPS level—an observation in line with the high prevalence of atherosclerosis in renal failure patients. In our study, the plasma LPS level was 0.44 ± 0.18 EU/ml, or 80 ± 36 pg/ml, which is higher than the median value of 14.3 pg/ml, as reported in patients with recurrent bacterial infection (12), but similar to the level observed in renal failure subjects undergoing hemodialysis (28) as well as patients with AIDS (15).

Our study supports the hypothesis that endotoxemia is related to accelerated atherosclerosis. Although there is a wealth of literature on this area, most of the published studies used endothelial or vascular dysfunction as a surrogate marker of atherosclerosis (13,29,30), whereas our study used carotid IMT—a more robust tool for quantifying atherosclerosis. In addition to an inverse correlation with serum albumin level (which is arguably a marker of inflammation rather than malnutrition), we did not find any correlation between circulating LPS levels and nutritional indices—another important component of the malnutrition-inflammation-atherosclerosis syndrome (31)—but our sample size was small and a clinically relevant correlation could have been missed. It remains possible that endotoxemia is part and parcel of the malnutrition-inflammation-atherosclerosis syndrome.

In our previous study (20), we showed that carotid IMT correlated with patient age, serum LDL level, Charlson's comorbid score, and serum CRP. Carotid IMT was also significantly higher in diabetic than nondiabetic subjects. Of note, although carotid IMT significantly correlated with both serum LPS ($r = 0.415$) in the study presented here and CRP ($r = 0.279$) in the previous study (20), the correlation coefficient was substantially higher in the former, suggesting that carotid IMT is more affected by LPS than by CRP. Because the sample size was small in this study, we did not perform multivariate analysis to determine the independent predictors of carotid IMT. On the basis of a multiple linear regression analysis of the data from the previous study (20), age, serum LDL level, serum CRP, and diabetic status were independently associated with carotid IMT (unpublished analysis from our previous study (20)).

Because of the limitation in the original study design, we cannot confirm the cause of endotoxemia in our patients. Because endotoxemia has been reported in hemodialysis patients (28,32), it seems probable that uremia *per se* is the cause. As to the source of endotoxin, occult infection is often implicated. However, none of the patients in this study had an indwelling vascular catheter at the time of the blood test or a history of peritonitis (as they were newly started on PD). Recently, Brenchley *et al.* (15) showed that microbial translocation from the gastrointestinal tract is the cause of endotoxemia and systemic immune activation in AIDS patients. Further study is needed to determine whether the same pathologic process exists in renal failure patients.

There are several other important inadequacies in our study and our result can only be considered preliminary. The sample size was small and the study was purely cross-sectional. Although we demonstrated a correlation between circulating LPS level and carotid IMT, which has been found to be an important predictor of CVD in dialysis (33–35) as well as predialysis renal failure patients (20), further prospective study is needed to determine whether a high circulating LPS level could predict CVD, and, if that is the case, whether the effect is mediated via arterial wall thickening as revealed in carotid IMT.

Another aspect that is worth further investigation is the potential benefit of treatment. Recent reports suggest that endotoxin-related inflammation and vascular abnormality is reversible. Statin has been found to inhibit endotoxin-induced vascular inflammation, which may contribute to the therapeutic role in atherosclerotic diseases (29). Selective intestinal decontamination partially reverses the hyperdynamic circulatory state in cirrhotic patients (36). Before embarking on therapeutic trials, however, it seems logical to clarify the origin of endotoxemia in renal failure patients so that targeted therapy can be designed.

In summary, we found that endotoxemia was common in PD patients, and the degree of circulating endotoxemia was related to the severity of systemic inflammation and features of atherosclerosis. Our result suggests that endotoxemia may contribute to the systemic inflammatory state and accelerated atherosclerosis in PD patients.

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Disclosures

None.

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