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Association of inflammation and protein-energy wasting with endothelial dysfunction in peritoneal dialysis patients

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Abstract

Background. Cardiovascular disease is the main cause of mortality in end-stage renal disease (ESRD) patients. Recent studies have indicated that non-traditional risk factors such as endothelial dysfunction (ED), chronic inflammation and protein-energy wasting (PEW) may contribute significantly to the increased cardiovascular mortality among dialysis patients. To further ascertain this association, we carried out a cross-sectional assessment of nutritional status, inflammatory markers and endothelial dysfunction in peritoneal dialysis (PD) patients.

Methods. We measured ED functionally by flow-mediated vasodilatation (FMD) using doppler ultrasonography and biochemically by soluble intercellular adhesion molecule-1 (sICAM-1) in 105 stable PD patients and 32 age- and sex-matched healthy controls. We also simultaneously measured inflammatory markers and performed a subjective global assessment (SGA) of their nutritional status using a seven-point scoring scale. Subjects were subgrouped according to their nutritional and inflammatory status.

Results. In PD patients, FMD was markedly lower (9.9±4.8% *vs.* 16.4±4.8%, $P<0.05$), and sICAM-1 was significantly higher than those in controls. The malnourished patients had significantly lower FMD (8.4±4.6% *vs.* 10.8±4.7%, $P<0.05$) and higher sICAM-1 than the nourished patients. The inflamed group had significantly lower FMD (7.1±3.8 *vs.*11.1±4.6%, $P<0.05$) and higher sICAM-1 than the non-inflamed group. In all PD patients, lean body mass/body weight %, albumin and SGA correlated positively with FMD ($r = +0.207$, $r = +0.224$, $r = +0.285$, $P<0.05$). However, age, log high sensitivity C-reactive protein (hsCRP), log IL-6 and sICAM-1 were negatively correlated with FMD ($r= -0.275$, $r = -0.361$, $r = -0.360$, $r = -0.271$, $P<0.05$). A multiple regression analysis showed that log hsCRP was an independent factor affecting FMD. Endothelial function, demonstrated as FMD and sICAM-1 in the nourished PD patients without inflammation, was well preserved compared to other subgroups.

Conclusion. Our data suggest that chronic inflammation and PEW are closely linked to ED in PD patients.

Keywords: endothelial dysfunction; inflammation; peritoneal dialysis; protein-energy wasting

Introduction

Atherosclerotic cardiovascular disease (ACVD) is the main cause of mortality in end-stage renal disease (ESRD) patients, as shown in data from the US Renal Data System. In ESRD patients, mortality rates due to cardiovascular disease are 10 to 30 times higher than those in the general population [1]. Moreover, there is more that attributes to this high mortality rate for dialysis patients than just traditional risk factors of ACVD such as hypertension, diabetes mellitus, cigarette smoking and dyslipidaemia. In this regard, it is important to analyse the association between non-traditional risk factors, such as inflammation, protein-energy wasting (PEW) and endothelial dysfunction (ED), and the increased mortality rate in ESRD patients [2].

PEW is the state of decreased body stores of energy fuels such as protein and fat [3]. ESRD patients revealed chronic inflammation, loss of blood and nutrients into dialysate, recurrent catabolic illness and metabolic syndrome resulting in loss of lean body mass (LBM). PEW is prevalent in both predialysis and dialysis patients and might be associated with higher rate of mortality due to ACVD [3–5].

Inflammation, as evidenced by the elevated C-reactive protein (CRP) and proinflammatory cytokine levels, has been shown to predict wasting illness, cardiovascular mortality, hospitalization and death in dialysis patients [2,6–11].

Table 1. Characteristics of the control group and the PD patient group

	Control group (n=32)	PD patient group (n=105)	P value
Age (years)	48.7±5.6	51.5±11.2	0.450
Sex (male:female)	14 : 18	47 : 58	0.839
PD duration (months)		87.6±49.3	
ACEi or ARB use (yes, n)		79	
BMI (kg/m^2)	23.6±2.8	24.2±3.3	0.392
Systolic blood pressure (mmHg)	125.0±15.4	147.7±19.7	0.000
Total cholesterol (mg/dL)	190.3±38.2	192.4±39.0	0.782
HDL cholesterol (mg/dL)	57.8±14.9	47.4±31.9	0.077
Triglyceride (mg/dL)	123.3±70.5	161.3±121.3	0.000
Fasting glucose (mg/dL)	81.1±13.2	93.3±16.0	0.000
Protein (g/dL)	7.1±0.5	6.1±0.6	0.000
Albumin (g/dL)	4.4±0.2	3.5±0.4	0.000
Log hsCRP	−0.23±0.52	0.11±0.70	0.011
Log IL-6	0.13±0.37	0.83±0.28	0.000
sICAM-1 (ng/mL)	260.4±84.0	343.1±120.7	0.000
FMD (%)	16.4±4.8	9.9±4.8	0.000
NMD (%)	22.6±5.9	16.4±7.2	0.000

Data are expressed as mean±SD. Means were tested by unpaired t-test. P values compare the control group and PD patient group. PD, peritoneal dialysis; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; FMD, flow-mediated vasodilatation; NMD, nitroglycerine-mediated vasodilatation.

ED is considered an early marker for atherosclerosis and is associated with an increased mortality risk in patients with both ischaemic and non-ischaemic chronic heart failure [2,10–18]. Several studies have shown that ED was impaired in predialysis [19,20] and dialysis patients [21–26]. Although ED was reported to be impaired in ESRD patients, any association between inflammation and nutritional status in impaired endothelial function has not been studied.

In this study, we carried out a cross-sectional study to investigate whether PEW and chronic inflammation play an important role in ED in peritoneal dialysis (PD) patients.

Materials and methods

Subjects

This study enrolled 105 ESRD patients who had maintained PD treatment for more than 6 months prior to this study and had been adequately dialysed. We excluded those who had acute inflammation such as fever or PD-related infection (e.g. exit site infection, tunnel infection and PD peritonitis) within 2 months and patients with malignancies.

We also included healthy control subjects (n=32) who were matched for gender and age. These control subjects did not have any history of hypertension, diabetes mellitus, renal or vascular disease and were receiving no drugs at the start of the study.

Study procedure

This was a cross-sectional study. Subjects were checked for inflammation markers such as high sensitivity CRP (hsCRP) and interleukin-6 (IL-6).

Simultaneously, we performed the subjective global assessment (SGA) of the nutritional status of the subjects using a seven-point scoring scale.

ED was evaluated by flow-mediated vasodilatation (FMD) using doppler ultrasonography and soluble intercellular adhesion molecule-1 (sICAM-1).

A medical history and a physical examination such as gender, the duration of PD treatment, blood pressure, height, weight, body mass index (BMI, kg/m^2) and LBM were done. LBM was determined by creatinine kinetics.

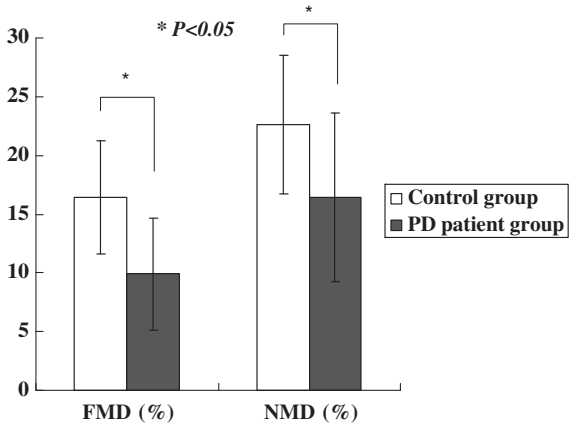

Fig. 1. Endothelium-dependent vasodilatation (FMD) and endothelium-independent vasodilatation (NMD) of the brachial artery in the PD patient group and the control group. FMD, flow-mediated vasodilatation; NMD, nitroglycerine-induced vasodilatation; PD, peritoneal dialysis.

Blood samples were collected after at least 12 h of fasting on the day of brachial artery FMD. We measured the level of total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, fasting glucose, total protein and albumin. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. hsCRP was measured by nephelometry. Serum IL-6 and sICAM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA, R&D System Europe Ltd, Abingdon, UK).

Brachial artery FMD

Patients stopped taking caffeine and any other medications, including antihypertensive agents, at least 12 h prior to FMD assessment. Brachial artery FMD was measured with a high-frequency (GE LOGIQ 9, 10 MHz) ultrasound scanning probe to obtain longitudinal images of the brachial artery at a marked point 5 to 10 cm proximal to the antecubital fossa. At first, the baseline end-diastolic diameter was measured. After this, the cuff was inflated to 50 mmHg higher than the systolic BP and was positioned at the proximal upper extremity. After 5 min, the cuff was deflated, and the arterial diameter was measured 1 min after the cuff was deflated. After 10 min, 0.6 mg of sublingual nitroglycerine was administered, and the arterial diameter was measured 5 min later to obtain nitroglycerine-mediated vasodilatation (NMD) to differentiate endothelium-dependent from smooth-muscle effects. FMD and NMD were calculated as below.

We measured the diameter of the brachial artery on two occasions by one observer (intra-observer variability), and another observer independently performed the determination for the same patients (inter-observer variability) to test the reliability of FMD measurements [27]. The intra-observer variability was 0.06±0.04 mm, and the inter-observer variability was 0.08±0.07 mm.

FMD (%) = [(RH-EDD) − (B-EDD)]/B-EDD × 100

NMD (%) = [(N-EDD) − (B-EDD)]/B-EDD × 100.

B-EDD, baseline end-diastolic diameter; RH-EDD, end-diastolic diameter during reactive hyperaemia; N-EDD, nitroglycerine-induced end-diastolic diameter; FMD, flow-mediated vasodilatation; NMD, nitroglycerine-mediated vasodilatation.

Subgroup analyses

Subjects were divided into subgroups according to their nutritional and inflammatory status. Patients having hsCRP≥3.0 mg/L were grouped as inflamed and those with an SGA score lower than 5 as malnourished. To compare the compound effects of inflammation and PEW in patients, we subgrouped patients according to the categories below:

N−I: nourished without inflammation, patients having hsCRP< 3.0 mg/L and SGA score >5

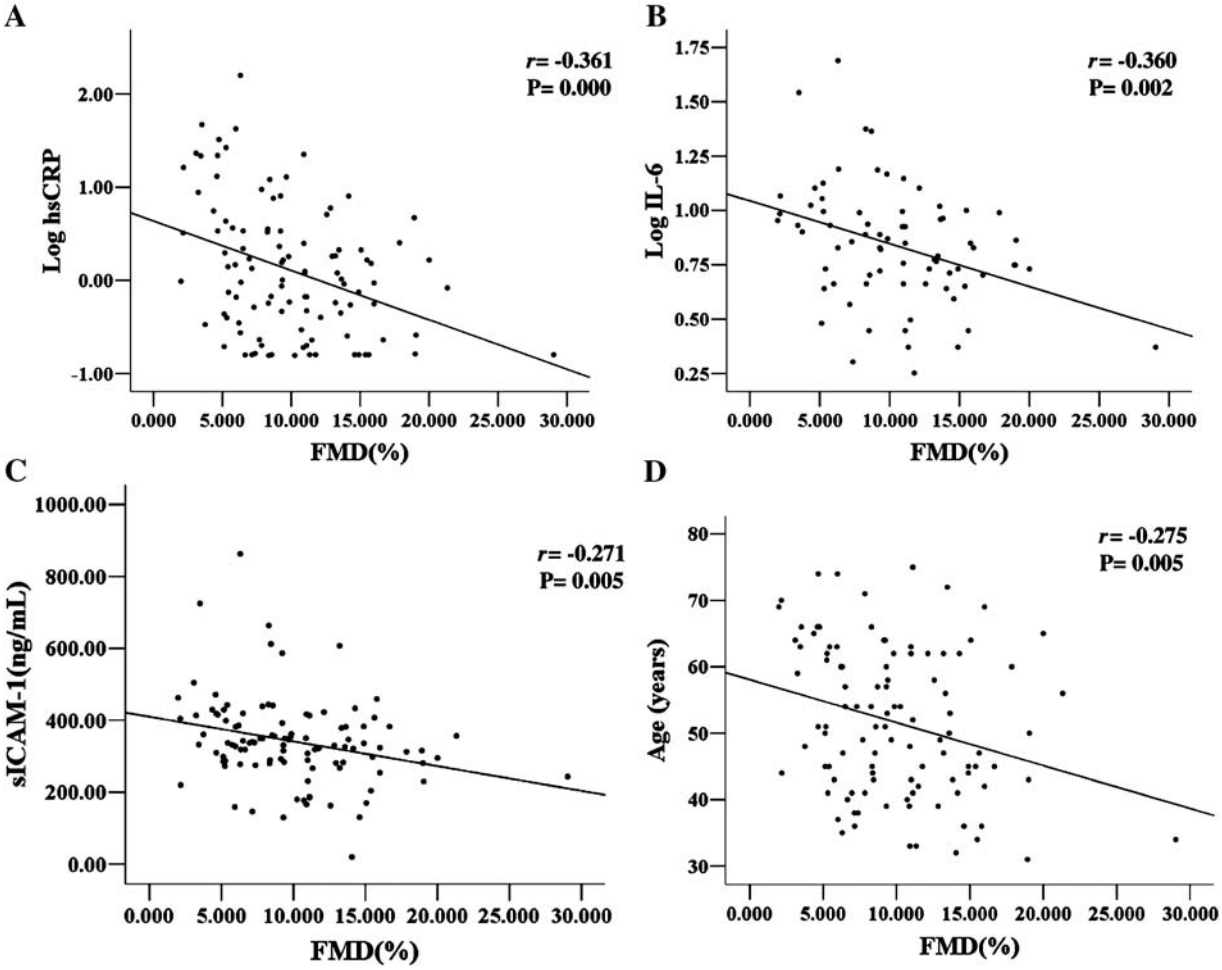

Fig. 2. Correlation between FMD and log hsCRP levels (A), log IL-6 levels (B), sICAM-1 (C) and age (D) in the entire PD patient group.

N+I: nourished with inflammation, patients having hsCRP≥3.0 mg/L and SGA score >5

M−I: malnourished without inflammation, patients having hsCRP< 3.0 mg/L and SGA score ≤5

M+I: malnourished with inflammation, patients having hsCRP≥ 3.0 mg/L and SGA score ≤5

Statistical analysis

Statistical analysis was performed using SPSS® version 13.0 (SPSS, Chicago, IL, USA). Simple comparisons of two or four groups were carried out using an unpaired *t*-test or ANOVA. Pearson's correlation coefficient was used for comparison between pairs of variables. Multiple regression analysis was used to determine the interaction between independent variables and the influence of cofounders. Data are shown as mean±standard deviation, unless otherwise stated. Statistical analysis of hsCRP and IL-6 was performed using log-transformed values, due to abnormal distribution. A value of *P* less than 0.05 was considered significant.

Results

Patients and control group

The PD patient group included 47 men and 58 women with a mean age of 51.5±11.2 years. All patients were on a four- to five-exchange per day PD regimen. Seventy-nine patients had taken angiotensin II-receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors.

Systolic blood pressure, fasting serum glucose and triglyceride were significantly higher, whereas serum protein and albumin levels were lower in the PD patient group than in the control group. Log hsCRP, log IL-6, and sICAM-1 levels were significantly higher in the PD patient group than in the control group (Table 1). PD patients were found with markedly lower FMD and NMD (9.9±4.8% *vs*. 16.4±4.8%, $P<0.05$, 16.4±7.2% *vs*. 22.6±5.9%, $P<0.05$) (Figure 1).

Nourished and malnourished groups in patients

Table 2 shows the clinical characteristics and biochemical findings of the patients who were grouped by their SGA scores. Thirty-eight patients (36.2%) were malnourished. BMI and serum albumin levels were significantly lower in the malnourished group. Log hsCRP and sICAM-1 levels were significantly higher in the malnourished group than in the nourished group. The malnourished group showed significantly lower FMD and NMD values than the nourished group (8.4±4.6% *vs.*10.8±4.7%, $P<0.05$, 14.4±6.6% *vs.* 17.4±7.3%, $P<0.05$) (Table 2).

Table 2. Characteristics of the nourished group and the malnourished group

	Nourished (n=67)	Malnourished (n=38)	P value
Age (years)	50.9±11.6	53.3±11.6	0.313
PD duration (months)	81.1±47.2	99.5±51.5	0.076
ACEi or ARB use (yes, n)	52	27	0.487
BMI (kg/m^2)	24.7±3.1	23.3±3.3	0.029
Systolic blood pressure (mmHg)	145.6±18.3	152.5±21.7	0.095
LBM/BW %	73.8±11.0	71.9±11.5	0.423
Total cholesterol (mg/dL)	193.5±40.7	190.3±38.2	0.684
HDL cholesterol (mg/dL)	50.2±38.9	42.0±10.4	0.218
Triglyceride (mg/dL)	165.8±137.8	154.9±87.4	0.668
LDL cholesterol (mg/dL)	110.2±48.6	117.3±31.4	0.563
Fasting glucose (mg/dL)	91.9±14.2	96.8±18.8	0.139
Protein (g/dL)	6.0±0.5	5.9±0.5	0.773
Albumin (g/dL)	3.6±0.4	3.4±0.4	0.008
Log hsCRP	0.003±0.626	0.295±0.793	0.039
Log IL-6	0.799±0.230	0.909±0.327	0.095
sICAM-1 (ng/mL)	319.4±104.5	386.1±142.1	0.008
FMD (%)	10.8±4.7	8.4±4.6	0.014
NMD (%)	17.4±7.3	14.4±6.6	0.038

Data are expressed as mean±SD. Means were tested by unpaired t-test. P values compare the nourished group and the malnourished group. LBM/BW %, lean body mass/body weight %.

Non-inflamed and inflamed patient groups

Of the total, 75 patients (71.4%) had hsCRP less than 3 mg/L ('the non-inflamed group'), whereas 30 patients (28.6%) had hsCRP higher than 3 mg/L ('the inflamed group'). The inflamed group was treated with PD for a longer period than the non-inflamed group. The inflamed group had higher levels of age, log hsCRP, log IL-6 and sICAM-1 and lower serum albumin and LBM/body weight (BW) % than those in the non-inflamed group (Table 3). Similar to the malnourished PD patients, the inflamed group also revealed significantly lower FMD and NMD than the non-inflamed group (7.1±3.8% *vs*.11.1±4.6%, P<0.05, 14.0 ± 5.3% *vs*. 17.4 ± 7.7%, P< 0.05) (Table 3).

Table 3. Characteristics of the non-inflamed group and the inflamed group

	Non-inflamed (n=75)	Inflamed (n=30)	P value
Age (years)	49.4±56.6	56.6±11.3	0.002
PD duration (months)	79.1±44.6	110.4±54.6	0.011
ACEi or ARB use (yes, n)	58	21	0.459
BMI (kg/m^2)	23.9±3.0	24.9±3.7	0.135
Systolic blood pressure (mmHg)	148.5±20.4	145.9±17.8	0.549
LBM/BW %	75.1±11.1	68.6±10.0	0.006
Total cholesterol (mg/dL)	194.2±40.9	188.1±34.0	0.463
HDL cholesterol (mg/dL)	46.5±13.4	49.6±55.9	0.649
Triglyceride (mg/dL)	156.4±123.7	173.4±116.4	0.513
LDL cholesterol (mg/dL)	116.4±38.2	103.8±52.7	0.926
Fasting glucose (mg/dL)	91.9±14.2	96.8±18.8	0.081
Protein (g/dL)	6.1±0.6	5.9±0.5	0.272
Albumin (g/dL)	3.6±0.4	3.4±0.5	0.018
Log hsCRP	−0.251±0.402	1.007±0.428	0.000
Log IL-6	0.762±0.230	1.057±0.268	0.000
sICAM-1 (ng/mL)	316.9±93.3	407.3±154.1	0.000
FMD (%)	11.1±4.6	7.1±3.8	0.000
NMD (%)	17.4±7.7	14.0±5.3	0.027

Data are expressed as mean±SD. Means were tested by unpaired t-test. P values compare the non-inflamed group and the inflamed group.

Table 4. Multiple regression analysis for the determinants of the independent factors affecting FMD

	ß	P value
Lean body mass/body weight %	0.019	0.866
SGA	0.134	0.205
Albumin (g/dL)	0.086	0.410
Age (years)	−0.092	0.418
Log hsCRP	−0.221	0.045
sICAM-1 (ng/mL)	−0.077	0.481

SGA, subjective global assessment; ß, standardized ß coefficient. The dependent factor of multiple regression analysis was FMD (%).

Correlations and compound analysis affecting FMD

In Pearson's correlation analysis of the whole PD patient group, LBM/BW %, albumin and SGA correlated positively with FMD (r = +0.207, r = +0.224, r = +0.285, P<0.05). However, log hsCRP, log IL-6, sICAM-1 and age showed significant negative correlations with FMD (r = −0.275, r = −0.361, r = −0.360, r = −0.271, P<0.05) (Figure 2).

A multiple regression analysis showed that log hsCRP was an independent factor affecting FMD (Table 4).

The subgroup analysis was performed to investigate compound effects of the nutritional and inflammatory status of patients. As a result, the nourished without inflammation group showed the highest FMD (N−I, 11.8±4.5%; N+I, 7.1±4.2%; M−I, 9.4±4.8%; M+I, 6.9±3.5%; P<0.05) and the lowest sICAM-1 levels (N−I, 301.3±99.9 ng/mL; N+I, 383.5±97.3 ng/mL; M−I, 351.2±68.4 ng/mL; M+I, 429.6±193.8 ng/mL; P<0.05) among the four subgroups. However, no significant differences were found between the group with only PEW and the group with only inflammation (Figure 3).

Discussion

This study is the first to show the compound relationships between the nutritional and inflammatory status and ED in PD patients.

Annual mortality due to ACVD in ESRD patients is 10 to 30 times higher than in the general population, even with adjusted age, gender and the presence of diabetes [28,29]. Traditional risk factors for ACVD such as age, diabetes mellitus, hypertension and dyslipidaemia are common risk factors for ESRD patients as they are well established in the general population. However, several studies on the association of traditional risk factors with cardiovascular mortality in ESRD patients did not have similar results to those in the general population. Non-traditional risk factors for ACVD, such as PEW, inflammation, vascular calcification, oxidative stress and hyperhomocysteinaemia are commonly found in chronic renal failure patients. Based on recent studies, these factors may be closely linked to the acceleration of ACVD in ESRD patients [30].

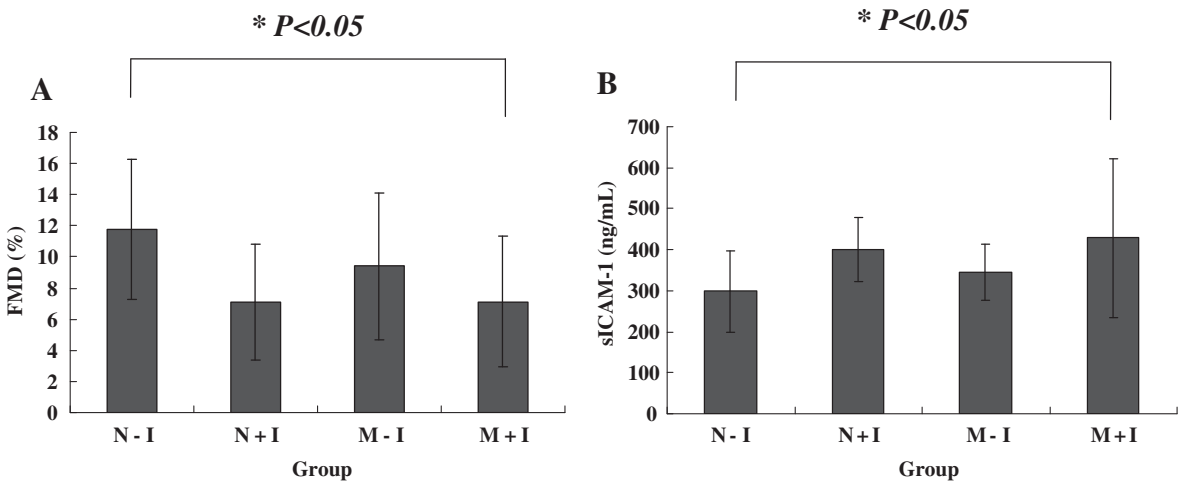

Fig. 3. FMD (A) and serum sICAM-1 levels (B) in four subgroups. N−I, nourished without inflammation; N+I, nourished with inflammation; M−I, malnourished without inflammation; M+I, malnourished with inflammation.

In this study, we determined non-traditional risk factors such as PEW, chronic inflammation and ED in PD patients compared to in control subjects. In addition, the present study revealed the correlations among the level of systemic inflammatory markers, the nutritional status and ED in PD patients.

To determine which factor influences impaired ED more profoundly, we performed the subgroup analysis of ED according to the nutritional and inflammation status. The subgroup without PEW and chronic inflammation presented the most conserved endothelial function compared to other subgroups. ED was not significantly different between the group with only PEW and the group with only inflammation.

Taken together, these findings suggested that PEW and inflammation are closely associated with the development of ED and provided evidence that PEW, inflammation and ED coexist in PD patients.

The important role of ED has been well demonstrated in the pathogenesis of atherosclerosis. Endothelial function can be assessed by monitoring the vasodilatation produced by the administration of endothelium-dependent agonists such as acetylcholine or by increased blood-flow shear (as flow-mediated vasodilatation) [12,15,16].

Van Guldener C *et al*. first described the endothelium-dependent vasodilatation impairment in chronic haemodialysis (HD) patients [21] and in peritoneal dialysis patients [22]. ED was reported to be correlated with coronary risk factors such as hypertension [31,32], age [33] and hypercholesterolaemia [34] in the general population. However, van Guldener C *et al*. reported that ED in PD patients only correlated with a mean arterial pressure, not with age, gender and total cholesterol levels. Our study showed that FMD is significantly correlated with age but not with systolic blood pressure and total cholesterol levels in PD patients, among the major risk factors for coronary artery disease. Contrary to the associations with major coronary risk factors, ED in PD patients correlated with non-traditional coronary risk factors such as hsCRP, IL-6, low serum albumin levels and PEW in this study.

Thus far, the findings of endothelium-independent vasodilatation have been different in chronic kidney disease (CKD) and ESRD patients [21,22,35–39]. Van Guldener *et al*. reported that endothelium-independent vasodilatation was not different in ESRD patients compared to the control group [21,22]. However, Joannides *et al*. demonstrated that endothelium-independent vasodilatation was lower in HD patients than in the control group [37]. These discrepancies cannot be easily explained, but they are attributable to different characteristics and sizes of the study populations and methodologies. Our study showed that endothelium-independent vasodilatation, demonstrated as 'NMD', was reduced in PD patients compared to the control group and that it was closely associated with FMD. In particular, both FMD and NMD were significantly lower in the malnourished PD patients than the nourished PD patients. On the other hand, the inflamed PD patients had lower FMD and NMD than the non-inflamed PD patients did.

Although we did not investigate the vascular calcification markers in subjects, the impairment of NMD in PD patients seemed to imply that vascular calcification or vessel stiffness played a role in the development of ED in this study [35,40–42].

ICAM-1 was considered the reliable marker of ED [43]. Previous studies reported an association of ICAM-1 with atherosclerotic plaque and outcome of dialysis patients [25,26]. This study showed a significant correlation between sICAM-1 and FMD. However, the multiple regression analysis did not show sICAM-1 as the factor affecting FMD.

In conclusion, this study showed impaired endothelial function in PD patients in comparison with the control group. We identified age, albumin, chronic inflammation and PEW as being closely linked to ED in PD patients. PD patients who had a good nutritional status and no inflammation were found with well preserved endothelial functions.

This study implied that the risk assessment integrating non-traditional risk factors could play an important role in predicting and designing detailed therapy strategies for preventing ACVD mortality in ESRD patients.

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Conflict of interest statement. None declared.

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