Original Article

Peritoneal Protein and Albumin Excretion as Markers of Cardiovascular Risk and Systemic Endothelial Dysfunction

Cheuk-Chun Szeto, Kai-Ming Chow, Kwok-Yi Chung, Bonnie Ching-Har Kwan, Philip Kam-Tao Li

Background: Microalbuminuria is a marker of systemic endothelial dysfunction. We studied the relationship between peritoneal protein loss in peritoneal dialysis (PD) patients, which is conceptually analogous to microalbuminuria in non-uremic patients, and pre-existing vascular disease in new PD patients.
Methods: Peritoneal total protein and albumin loss were quantified within 2 months of initiation of dialysis in 44 consecutive new PD patients, together with a standard peritoneal equilibration test. The results were compared according to the presence of cardiovascular disease (CVD) prior to initiation of dialysis, lean body mass, and serum albumin and C-reactive protein (CRP) concentrations.
Results: The dialysate albumin concentration was closely correlated with the creatinine dialysate-to-plasma ratio at 4 hours ($r = 0.601$, $p < 0.001$). It was higher in patients with pre-existing CVD than in those without, when patients were analyzed according to diabetic status (one-way ANOVA, $p = 0.004$). In diabetic patients, the dialysate albumin concentration was significantly higher in patients with pre-existing CVD than in those without (0.754 ± 0.273 vs 1.088 ± 0.280 mg/μmol creatinine, $p = 0.04$). Multivariate analysis showed that only diabetic status and dialysate albumin concentration, but not peritoneal transport status or serum CRP, were independent predictors of pre-existing CVD. Although dialysate protein loss accounted for only 10.5 ± 4.4% of total protein catabolism, the dialysate protein level was significantly correlated with serum albumin concentration ($r = –0.457$, $p = 0.002$), percentage of lean body mass ($r = –0.558$, $p < 0.001$), and serum CRP concentration ($r = 0.434$, $p = 0.003$).
Conclusions: Patients with CVD prior to initiation of dialysis have higher levels of dialysate albumin and total protein excretion, indicating that dialysate protein loss is a marker of underlying CVD. Dialysate protein and albumin excretion may provide a simple and convenient measure of vascular disease and endothelial dysfunction in PD patients. [*Hong Kong J Nephrol* 2004;6(1):31–7]

Key words: atherosclerosis, inflammation, peritoneal dialysis

背景: 微白蛋白尿症是系統性內皮功能障礙的指標。腹膜透析 (PD) 接受者之蛋白流失，在概念上與非尿毒症患者之微白蛋白尿症類似。本研究調查了在剛開始 PD 的病人中，腹膜性蛋白流失與既有血管性疾病的關係。
方法: 研究人員以 44 位剛開始接受 PD (2 個月內) 的病人為對象，測量腹膜性總蛋白及白蛋白之流失，同時進行標準之腹膜平衡試驗；再將有關數據按病人之各項特徵作出比較，包括心血管疾病 (CVD) 於 PD 開始前的存在與否、身體瘦肉質量、及白蛋白與 CRP (C-reactive protein) 血清濃度。
結果: 透析液之白蛋白濃度、與 4 小時之透析液/血漿肌酸酐比例呈正相關性 ($r = 0.601$, $p < 0.001$)。根據糖尿病狀態作分析，可見腹膜性蛋白流失與既有血管性疾病有關 (one-way ANOVA, $p = 0.004$)；在患有糖尿病的病人間，與非 CVD 患者相比，CVD 患者的透析液白蛋白濃度出現顯著增加 (0.754 ± 0.273 vs 1.088 ± 0.280 mg/μmol 肌酸酐, $p = 0.04$)。多變項分析顯示，糖尿病狀態及透析液白蛋白濃度，而非腹膜運輸狀態或血清 CRP，可作為既有 CVD 的獨立預測因子。雖然自透析液的流失僅佔蛋

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白質分解代謝總量之 10.5 ± 4.4%，透析液之蛋白濃度仍與血清白蛋白濃度 ($r = –0.457$, $p = 0.002$)、身體瘦肉質量百分比 ($r = –0.558$, $p < 0.001$)、及血清 CRP 濃度 ($r = 0.434$, $p = 0.003$) 呈顯著相關性。結論: 對於在開始接受透析治療前已出現 CVD 的病人，腹膜性總蛋白及白蛋白的流失高於非患者，顯示腹膜性蛋白流失可作為既有 CVD 的指標。因此，腹膜性蛋白流失的測量，可望為 PD 接受者的血管性疾病及內皮功能障礙，提供一個簡便的評估方法。

Introduction

Inflammation plays a pivotal role in the pathogenesis of atherosclerotic disease and malnutrition [1,2]. Elevated plasma C-reactive protein (CRP) concentrations, induced by other pro-inflammatory cytokines, are associated with the risk of myocardial infarction [3] and mortality [4] in peritoneal dialysis (PD) patients. On the other hand, pro-inflammatory cytokines can cause protein catabolism and malnutrition [5–7]. Several studies have found that inflammation alone, or in combination with a low protein intake, causes hypoalbuminemia in dialysis patients [8,9]. The complicated interactions between malnutrition, inflammation and atherosclerotic diseases are now known as the MIA syndrome [10].

How does inflammation cause atherosclerosis? One possibility is that inflammation induces endothelial dysfunction which, at least in non-uremic patients, has important roles in the pathogenesis of atherosclerosis [11]. Endothelial dysfunction can be measured using a panel of serum markers (e.g. soluble intercellular adhesion molecule 1, sICAM-1, and vascular cell adhesion molecule 1, VCAM-1) [12–14], but all are expensive and none is applicable for routine clinical use. Interestingly, microalbuminuria potentially represents a simple and inexpensive marker of endothelial dysfunction [15]. The relationship between microalbuminuria and cardiovascular disease (CVD) was first noted in diabetic patients [16], but it has since been documented in non-diabetic populations [17,18]. Although the exact nature of this association is not fully understood, it has been proposed that microalbuminuria represents a systemic endothelial abnormality [15], affecting not only glomerular capillaries, but also arterial and arteriolar intimal function, thereby promoting transvascular escape of atherogenic molecules [19].

If microalbuminuria is a result of systemic endothelial dysfunction, we predict that peritoneal albumin loss in PD patients, which is conceptually analogous to microalbuminuria in non-uremic patients, would be a surrogate marker of endothelial dysfunction and a predictor of CVD in PD patients. This pilot study examined the relationship between peritoneal protein loss, pre-existing vascular disease and markers of systemic inflammation in new PD patients.

Patients and Methods

Patient selection

We studied consecutive new PD patients. Patients underwent a standard peritoneal equilibration test (PET) [20] within 2 months of the commencement of PD, when they were in a euvolemic state. On the day prior to PET, 24-hour urine and dialysate collection was performed to assess nutritional status. The presence of diabetes and a history of CVD at initiation of dialysis were recorded. CVD was defined as angina, class III–IV congestive heart failure, or a history of previous myocardial infarction, cerebrovascular accident or amputation for vascular disease.

Study of peritoneal transport

PET was performed using the method of Twardowski et al [20]. Briefly, a 4-hour dwell study was carried out with 2 L of dextrose 2.5% dialysis fluid (Dianeal, Baxter-Travenol, Deerfield, IL, USA). Dialysate creatinine and glucose concentrations were measured at 0, 2 and 4 hours, and plasma creatinine and glucose concentrations at 2 hours. Drainage and ultrafiltration volumes at 4 hours were documented. Creatinine dialysate-to-plasma ratios (D/P) at 0, 2, and 4 hours were calculated after correction for glucose interference. The results were plotted on a PET graph. Patients were classified into high, high-average, low-average, and low transporters, as described previously [20]. Mass transfer area coefficients (MTAC) of creatinine normalized for body surface area (BSA) were calculated using the formula described by Krediet et al [21]. BSA was determined by nomogram from body weight and height [22].

Peritoneal protein and albumin excretion rate

During PET, dialysate albumin and total protein concentrations at 4 hours were determined using a fully automated analyzer (Konelab 60, Thermo Clinical Labsystems, Thermo Electron Corporation, Waltham, MA, USA), and the concentrations were adjusted for dialysate creatinine concentration. In all measurements, creatinine concentration in the dialysate was corrected for glucose interference according to a formula provided by our laboratory [23].

Peritoneal protein loss, nutrition and inflammation markers

On the day prior to PET, 24-hour urine and dialysate collection was performed. Lean body mass was calculated according to the formula described by Forbes and Brunining [24], and normalized to percentage using the ideal body weight, determined from height and sex according to a standard formula validated in southern Chinese [25]. The protein catabolic rate was calculated using the modified Bergstrom's formula [26]. Daily protein loss in the dialysate was measured using a standard biochemical method. Serum albumin was measured using the bromcresol purple method. Serum CRP was measured with the Tina-quant CRP (Latex) ultra-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA) for Windows. Results are expressed as mean ± standard deviation unless otherwise specified. Comparisons between groups were performed using the Chi-squared test, Student's *t* test or Kruskal-Wallis test as appropriate. Correlations between continuous variables were examined using Pearson's correlation coefficient or Spearman's rank correlation coefficient, as appropriate. In order to explore the independent role of dialysate albumin concentration as a marker of inflammation and CVD, a backward stepwise logistic regression model was constructed with CVD as the dependent variable, and diabetes, creatinine D/P at 4 hours, serum CRP concentration and dialysate albumin concentration adjusted for creatinine as independent variables. A p value of less than 0.05 was considered significant. All probabilities were two-tailed.

Results

We studied 44 patients in total. Demographic and baseline clinical information are summarized in the Table. The average creatinine D/P at 4 hours was 0.628 ± 0.145, and the average MTAC of creatinine was 9.63 ± 6.10 mL/min. There were 11 (25.0%) low transporters, 16 (36.4%) low-average transporters, 11 (25.0%) high-average transporters, and six (13.6%) high transporters. The mean unadjusted dialysate albumin concentration was 311.0 ± 125.1 mg/L, and the dialysate total protein concentration was 502.0 ± 201.0 mg/L. The average total nucleated cell count in the dialysis effluent was 4.0 ± 0.7/mL.

Relationship between dialysate albumin concentration and peritoneal transport

After adjustment for dialysate creatinine concentration, the dialysate albumin concentration was closely correlated with creatinine D/P at 4 hours (Pearson's r = 0.601, $p < 0.001$) (Figure 1) and MTAC of creatinine ($r = 0.610$, $p < 0.001$), but not with the net ultrafiltration volume as determined by standard PET ($r = –0.08$, $p = 0.6$). Similarly, the dialysate total protein concentration was correlated with creatinine D/P at 4 hours ($r = 0.577$, $p < 0.001$) and MTAC of creatinine ($r = 0.563$, $p < 0.001$), but not with net ultrafiltration volume ($r = –0.13$, $p = 0.4$).

Table. Demographic and clinical data.

Number of patients	44
Gender (M/F)	18/26
Mean age ± SD (yr)	51.6 ± 14.7
Mean height ± SD (m)	1.63 ± 0.09
Mean weight ± SD (kg)	61.2 ± 13.7
Renal diagnosis, *n* (%)	
Glomerulonephritis	23 (52.3)
Diabetic nephropathy	12 (27.3)
Polycystic kidney	2 (4.5)
Obstructive uropathy	2 (4.5)
Others/unknown	5 (11.4)
Major comorbidity, *n* (%)	
Diabetes	14 (31.8)
Cardiovascular disease	16 (36.4)

Relationship between dialysate albumin concentration and CVD

Dialysate albumin concentration was marginally higher in new PD patients with pre-existing CVD than in those without (0.680 ± 0.253 vs 0.717 ± 0.265 mg/μmol creatinine), but the difference was not statistically significant. The difference became much more obvious when patients were analyzed according to their diabetic status (Kruskal-Wallis test, $p = 0.018$) (Figure 2A). In diabetic patients, the dialysate albumin concentration was significantly higher in patients with pre-existing CVD than in those without (0.754 ± 0.273 vs 1.088 ± 0.280 mg/μmol creatinine, $p = 0.04$). The dialysate total protein concentration was also greater in patients with pre-existing CVD than in those without (Kruskal-Wallis test, $p = 0.023$), although the magnitude of the difference was less remarkable.

Creatinine D/P at 4 hours was higher in new PD patients with pre-existing CVD than in those without (0.619 ± 0.144 vs 0.643 ± 0.149, $p = 0.6$). The difference remained statistically significant but clinically marginal when patients were analyzed according to diabetic

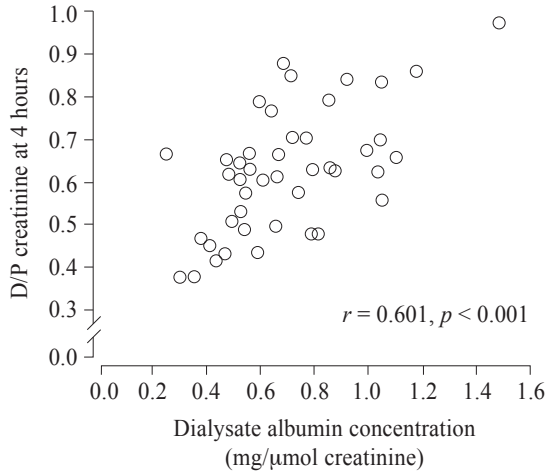

Figure 1. Correlation between creatinine dialysate-to-plasma ratio (D/P) at 4 hours of standard peritoneal equilibration test and dialysate albumin excretion.

status (Kruskal-Wallis test, $p = 0.012$) (Figure 2B). Multivariate logistic regression analysis showed that only diabetic status (adjusted odds ratio, OR, 40.7; 95% confidence interval, CI, 4.2–396.4; $p < 0.001$) and dialysate albumin concentration (adjusted OR, 1.01; 95% CI, 1.00–1.02; $p = 0.033$), but not creatinine D/P at 4 hours and serum CRP, were independent predictors of pre-existing CVD.

Relationship between dialysate albumin concentration and malnutrition

In our patients, the total daily protein loss in dialysate was 6.9 ± 3.0 g/day. In comparison, the total protein catabolic rate was 69.0 ± 28.0 g/day. Dialysate protein loss accounted for only 10.5 ± 4.4% of total protein catabolism. However, there were significant inverse correlations between dialysate protein loss and serum albumin concentration ($r = –0.457$, $p = 0.002$) (Figure 3A), and percentage lean body mass ($r = –0.558$, $p < 0.001$) (Figure 3B). Furthermore, dialysate protein loss had a significant correlation with serum CRP concentration (Spearman's $r = 0.334$, $p = 0.027$) (Figure 3C).

Discussion

In the present study, patients with CVD prior to initiation of dialysis had higher levels of dialysate albumin and total protein excretion, indicating that dialysate protein loss is a marker of underlying vascular disease and, as a consequence, of CVD, rather than the cause of chronic fluid overload. Furthermore, although dialysate protein loss makes only a small contribution to whole body protein catabolism, it is strongly correlated with nutritional indices and, more remarkably, is a marker of systemic inflammation.

Our finding provides an alternative explanation for the association between peritoneal transport status and morbidity in PD patients [27,28] (Figure 4). Traditionally, a high peritoneal transporter is believed to be

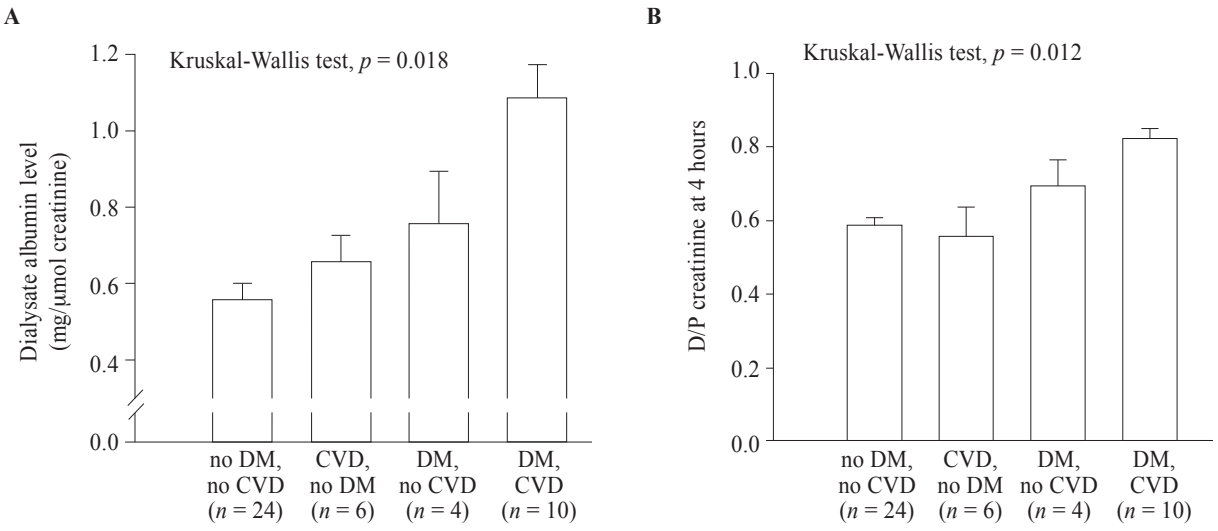

Figure 2. Stepwise increase in (A) dialysate albumin excretion and (B) creatinine dialysate-to-plasma ratio (D/P) at 4 hours of standard peritoneal equilibration test in patients with cardiovascular disease (CVD), diabetes mellitus (DM) and both conditions prior to initiation of dialysis.

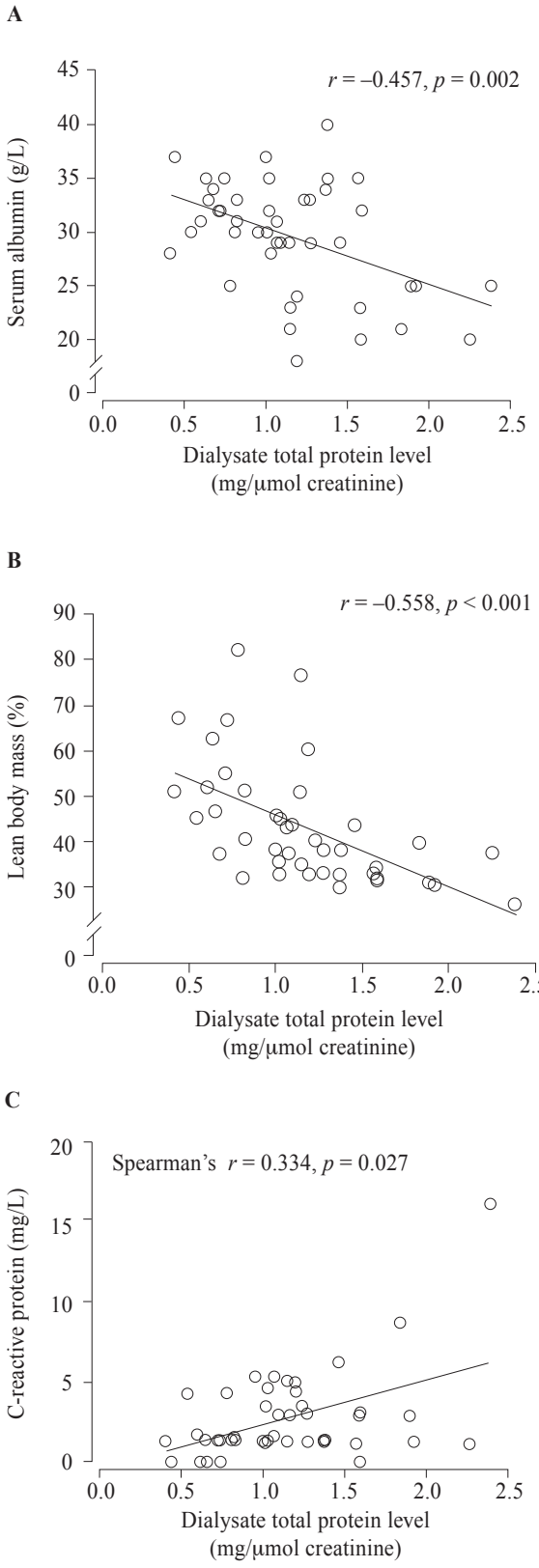

Figure 3. Relationship between dialysate total protein excretion and (A) serum albumin concentration, (B) percentage of lean body mass, and (C) serum C-reactive protein concentration.

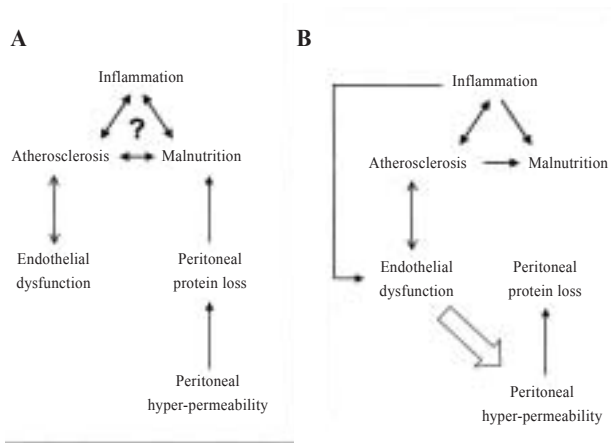

Figure 4. (A) Traditional view of MIA syndrome: malnutrition, inflammation and atherosclerosis have complicated interactions; peritoneal hyper-permeability is an independent event causing excessive protein loss in dialysis effluent, which results in malnutrition. (B) Our alternative explanation: inflammation induces endothelial dysfunction, which is closely linked to atherosclerosis. Endothelial dysfunction directly causes peritoneal hyper-permeability to macromolecules (broad arrow), which manifests as increased peritoneal protein loss. According to this model, peritoneal transport status to small molecules is a surrogate marker of peritoneal hyper-permeability to protein, accounting for the association between peritoneal transport and cardiovascular disease.

prone to fluid retention and peritoneal protein loss, which result in malnutrition and patient morbidity [27]. However, recent studies have shown that the association between peritoneal transport status and malnutrition exists before patients begin PD [28,29]. Our findings would certainly explain this intriguing observation.

Endothelial dysfunction in PD patients has become a hot topic in recent years. CVD and malnutrition are major causes of mortality and morbidity in PD patients [30,31]. In addition to the classic risk factors of atherosclerosis such as diabetes, hypertension and hyperlipidemia, uremia and possibly the dialysis procedure per se play important roles in the pathogenesis of accelerated atherosclerosis in renal failure patients [32]. However, the exact mechanisms by which uremia and dialysis cause CVD remain unclear. Recent studies have shown that endothelial dysfunction is an important marker of systemic vascular disease. In fact, the endothelium participates in a number of important homeostatic and cellular functions that are essential in preserving vascular functional integrity [33]. Endothelial dysfunction is responsible for inflammatory cell adhesion [34,35], an initial step in the atherosclerotic process, as well as the triggering of acute cardiovascular events [34,36]. In diabetic patients, plasma VCAM-1 levels correlate with the thickness of

the intimal plus medial layers of the carotid arteries [12], suggesting that the level of circulating VCAM-1 is a marker of atherosclerotic lesions [13,14].

Biochemical markers of endothelial dysfunction have been unsatisfactory. In response to pro-inflammatory cytokines, endothelial cells express sICAM-1 and VCAM-1 [37,38]. Increased levels of circulating adhesion molecules have been shown in patients suffering from inflammatory diseases and sepsis [39, 40]. In *in vivo* models, pro-inflammatory cytokines inhibit the formation of endothelium-dependent hyperpolarizing factor that may contribute to endothelial dysfunction [41]. In diabetic patients, an increased serum CRP concentration is associated with endothelial dysfunction [42]. Previous studies have shown that PD patients have impaired endothelium-dependent vasodilatation [43], but its relationship with inflammation in PD patients has not been studied in detail.

Our findings may provide new insight in the search for biochemical markers of endothelial dysfunction. Peritoneal albumin and protein excretion can be determined using the same assay as that used to screen for diabetic microalbuminuria, which is available in most hospital laboratories. Dialysate albumin excretion may provide a simple and convenient measure of endothelial dysfunction in PD patients. Further large-scale studies in this area are definitely needed.

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