ASSOCIATION OF NUTRITION STATUS AND PRO-INFLAMMATORY CYTOKINES IN PATIENTS WITH PERITONEAL DIALYSIS AT KING CHULALONGKORN MEMORIAL HOSPITAL, THAILAND

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ABSTRACT: Patients undergoing peritoneal dialysis (PD) are often malnourished. Elevated pro-inflammatory cytokine levels found during dialysis process may be a factor worsening nutritional status. This study was conducted to evaluate the relationship of the nutritional status and the levels of pro-inflammatory cytokines in patients undergoing PD at King Chulalongkorn Memorial Hospital, Bangkok. Anthropometry, biochemical measurement, and subjective global assessment (SGA) were performed. The levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α in plasma and spent dialysate were evaluated. There were 26 patients (13 males and 13 females) in this study. Based on the SGA scores, 13 patients (50.0%) were mildly-to-moderately malnourished, 2 (7.7%) were severely malnourished, and 11 (42.3%) were well nourished. The subjects with hypertension showed significantly higher concentration of plasma IL-6 compared to the subjects without hypertension (21.61 $\pm$ 9.42 *vs* 13.94 $\pm$ 0.35 pg/ml; $p < 0.05$). Plasma IL-6 concentration had positive correlations with body mass index ($r_s = 0.433$, $p = 0.027$) and mid-arm circumference ($r_s = 0.487$, $p = 0.012$). In addition, plasma IL-6 and TNF-α concentrations negatively correlated with dietary protein intake ($r_s = -0.414$, $p = 0.044$ and $r_s = -0.462$, $p = 0.022$ respectively). This study demonstrated that patients with PD tended to have malnutrition, and certain pro-inflammatory cytokines were observed in their plasma and spent dialysate. Early detection of malnutrition and of such cytokines could be beneficial in planning for therapeutic management.

Keywords: peritoneal dialysis, nutrition status, proinflammatory cytokines

INTRODUCTION

Patients with peritoneal dialysis (PD) treatment commonly suffer from malnutrition, which is a risk factor for increased mortality in these patients [1, 2]. Besides a high prevalence of malnutrition, PD patients also have high occurrence rate of inflammatory processes [3]. Increases in inflammatory biomarkers such as C-reactive protein, interleukin (IL)-6, and white blood cell count appeared to be linked with oxidative stress, cardiovascular disease, and malnutrition [4]. Inflammation initiates an acute-phase response, resulting in the activation of monocytes and/or macrophages, which in turn release two major cytokines: IL-1 and tumor necrosis factor (TNF)-α.

Both cytokines are the proximate initiators of the acute-phase response by stimulating the release of IL-6, which amplifies this acute-phase response. These cytokines then stimulate the inhibition of various protein synthesis in the liver, such as visceral proteins, albumin, pre-albumin, and transferrin. These proteins are traditionally considered markers of the nutritional status.

Many adverse nutritional impacts of the acute-phase response are mediated by the pro-inflammatory cytokines, primarily IL-6. The cytokine cascade has been implicated in anorexia and the depletion of visceral proteins by an anti-anabolic effect. TNF-α may suppress appetite and IL-6 induces muscle-wasting syndrome. These cytokines also stimulate muscle catabolism and inhibit muscle protein synthesis [5]. Malnutrition and inflammation are thus strongly related to each other and have effect

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Table 1 Anthropometry and laboratory data of the subjects

Parameters	Values[a]	% Standard
Body weight (kg)	62.77 ± 16.12	85.68 ± 20.79
MAC (cm)	28.54 ± 4.93	94.02 ± 15.36
MAMC (cm)	21.66 ± 2.94	89.18 ± 9.52
Body mass index (kg/m^2)	24.67 ± 5.26	
Serum albumin (g/dl)	3.51 ± 0.37	
Serum creatinine (mg/dl)	9.04 ± 3.61	
Dietary protein intake (g/kg/day)	0.98 ± 0.22	
Blood urea nitrogen (mg/dl)	52.76 ± 19.34	

[a] Values are expressed as mean ± standard deviation (SD).
MAC = mid-arm circumference; MAMC = mid-arm muscle circumference

on patient's outcome [3]. Previous studies inform strong association between the nutritional status and inflammatory markers in hemodialysis patients [6-8]; however, the information is still limited in PD patients. In addition, the correlations between pro-inflammatory cytokines in spent dialysate and the nutritional status is still unclear. Hence, this cross-sectional study was conducted to investigate the levels of proinflammatory cytokines IL-6 and TNF-α in plasma and spent dialysate, and their possible associations with nutritional status, in PD patients.

MATERIALS AND METHODS
The experimental protocol was approved by the Ethics Committee of Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all subjects before the study began. Twenty-six subjects aged older than 20 years old, who were treated with PD for more than 3 months at the Nephrology Unit, King Chulalongkorn Memorial Hospital participated in the study. All of them were clinically stable and did not present any active systemic inflammatory diseases, sign of infection or gastrointestinal problem. The nutritional status of the subjects was characterized following National Kidney Foundation (NKF) guidelines 2000 [9]. Subjective global assessment (SGA) and anthropometric measurements (body weight, mid-arm circumference (MAC), and mid-arm muscle circumference (MAMC)) were performed. Percentages of body weight, MAC, and MAMC were calculated based on standard values obtained from the National Health and Nutrition Examination Surveys II study with similar gender, height, age range and skeletal frame size. Body mass index (BMI) was also calculated. Blood samples were collected after a 12-hour fast for biochemical parameter determination and cytokine assay. In addition, 10 ml of spent dialysate was collected for cytokine assay. The concentrations of IL-6 and TNF-α in plasma and

spent dialysate were determined by enzyme-linked immunosorbent assay (ELISA) technique using specific antibody directed against the cytokine of interest (Duoset®, R&D Systems, USA). Kt/V was calculated from clearance of urea (K), dialysis time (t), and urea distribution volume (V) to quantify PD treatment adequacy based on NKF guidelines.

The data were expressed as mean ± standard deviation (SD) or median (minimum-maximum). When the data were not normally distributed, Mann-Whitney U test was used for selected comparison of the means between groups. Correlations were reported as the Spearman rank correlation coefficient (r_s). The significant level was set at 0.05.

RESULTS
Subject characteristics
The subjects included 13 male and 13 female patients aged between 29 to 81 years (62.38 ± 2.91 years old). All subjects were treated with PD more than 3 months (30.54 ± 8.89 months). Fourteen subjects (53.85%) were treated with continuous ambulatory peritoneal dialysis (CAPD), and 12 subjects (46.15%) were treated with automated peritoneal dialysis (APD). The etiologies of end-stage renal disease (ESRD) were diabetic nephropathy (46.15%), chronic glomerulonephritis (15.39%) and hypertensive nephrosclerosis (7.69%). However, the cause of ESRD in 8 subjects (30.77%) was not known.

Anthropometric and biochemical measurements
The results of anthropometric and biochemical measurements are given in Table 1. Based on the mean percentage of standard MAC, nutrition status of the subjects were normal. The mean percentages of standard body weight and MAMC was slightly lower than 90% indicating mild malnutrition. Based on Asian cut-off point criteria [10], the patients in this study were overweight. According to NKF

Table 2 Cytokine concentrations of the subjects based on peritoneal dialysis types, co-morbid diseases and peritoneal dialysis adequacy[a]

Groups	Plasma TNF-α (pg/ml)	Plasma IL-6 (pg/ml)	Dialysate IL-6 (pg/ml)
CAPD (n = 14)	34.09 (14.67-76.68)	16.51 (13.88-51.52)	19.37 (6.49-93.67) [*]
APD (n = 12)	31.13 (17.09-61.92)	17.10 (13.00-34.88)	9.60 (7.35-283.15)
DM (n = 13)	25.82 (17.09-76.68)	16.44 (13.00-34.88)	10.38 (7.35-93.67)
Non-DM (n = 13)	40.57 (14.67-61.92)	17.53 (13.78-51.52)	19.88 (6.49-283.15)
Dyslipidemia (n = 14)	32.46 (17.09-59.40)	17.19 (14.24-51.52)	15.83 (7.35-93.67)
Normolipidemia (n = 12)	32.31 (14.67-76.68)	16.41 (13.00-33.64)	15.35 (6.49-283.15)
Hypertension (n = 23)	32.15 (14.67-76.68)	17.53 (13.00-51.52) [*]	15.64 (6.49-283.15)
No Hypertension (n = 3)	32.47 (19.26-53.48)	13.78 (13.70-14.33)	18.45 (10.02-19.88)
Adequate dialysis (n = 14)	28.38 (14.67-57.52) [*]	15.55 (13.70-33.64) [*]	17.23 (6.49-283.15)
Inadequate dialysis (n = 12)	52.81 (24.46-76.68)	20.77 (13.00-51.52)	11.00 (7.35-26.58)

[a] Values are expressed as median (minimum-maximum).

[*] Significant difference between groups of the subjects based on peritoneal dialysis types, co-morbid diseases and peritoneal dialysis adequacy (Mann-Whitney U test, $p < 0.05$)

CAPD = continuous ambulatory peritoneal dialysis; APD = automated peritoneal dialysis; DM = Diabetes mellitus

Table 3 Correlations between cytokine concentrations and nutritional parameters[a]

Nutritional markers	Plasma TNF-α		Plasma IL-6		Dialysate IL-6	
	r_s	*p value*	r_s	*p value*	r_s	*p value*
Body weight (kg)	0.151	0.463	0.333	0.096	-0.093	0.652
Body mass index (kg/m^2)	0.132	0.519	0.433	0.027[*]	-0.127	0.538
MAC (cm)	0.193	0.344	0.487	0.012[*]	-0.034	0.871
MAMC (cm)	0.147	0.474	0.210	0.303	0.021	0.921
Dietary protein intake (g/kg/d)	-0.462	0.022[*]	-0.414	0.044[*]	-0.069	0.748
Serum creatinine (mg/dl)	-0.289	0.161	0.259	0.212	0.136	0.516
Serum albumin (g/dl)	-0.271	0.181	-0.133	0.519	-0.339	0.090

[a] Correlations are expressed as Spearman correlation coefficient (r_s).

[*] Significant correlation between cytokine concentrations and nutritional parameters ($p < 0.05$)

MAC = mid-arm circumference; MAMC = mid-arm muscle circumference

guidelines [9], the laboratory data revealed that serum albumin, serum creatinine, and dietary protein intake (DPI) of the subjects were below the normal ranges.

Subjective global assessment (SGA)
Based on SGA scores, 11 subjects (42.31%) appeared to have normal nutrition. Thirteen subjects (50.00%) were mildly-to-moderately malnourished, and 2 subjects (7.69%) were severely malnourished.

The levels of pro-inflammatory cytokines
Table 2 shows cytokine concentrations in the subjects, by peritoneal dialysis types, co-morbid diseases and PD adequacy. The level of TNF-α in spent dialysate was detectable in only 1 subject, so this parameter was not considered in analysis. There was no significant difference in any cytokine concentration between male and female subjects. When compared cytokine concentrations between the patients with continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), the results showed a significant difference in dialysate IL-6 between these groups ($p < 0.05$).

Subjects with hypertension had significantly higher concentration of plasma IL-6 than did subjects without hypertension ($p < 0.05$). According to Kt/V, plasma TNF-α and plasma IL-6 concentrations were higher with adequate dialysis than with inadequate dialysis ($p < 0.05$).

The correlations of cytokine concentrations and nutritional parameters are shown in Table 3. Levels of plasma IL-6, plasma TNF-α, and dialysate IL-6 were not correlated with each other. Plasma IL-6 concentration was positively correlated with several nutritional parameters including BMI ($r_s = 0.433$, $p = 0.027$) and MAC ($r_s = 0.487$, $p = 0.012$). However, it was negatively correlated with DPI ($r_s = -0.414$, $p = 0.044$). There was a significant negative correlation between plasma level of TNF-α and DPI ($r_s = -0.462$, $p = 0.022$).

DISCUSSION
This study investigated the levels of cytokines IL-6, and TNF-α in plasma and dialysate of PD patients. Relationships between nutritional parameters and the specific cytokines were also assessed in this

study. The presence of malnutrition, especially with co-morbid diseases, is a strong predictor of morbidity and mortality in the PD patients [11]. Hence, it is important to periodically monitor nutritional status for maintenance and recovery of health. In this study, nutritional assessment followed the NKF guidelines [9]. Anthropometry, biochemical parameters, and SGA were used to evaluate nutritional status, as these measurements provide a valid and clinically useful characterization of the nutritional status in dialysis patients [9].

MAC is simply performed to evaluate muscle and subcutaneous adipose tissue, while MAMC is an indicator of muscle. In the present study, %MAC was higher than 90% suggesting adequate muscle and fat in the PD patients. However, %MAMC of lower than 90% was found indicating low muscle protein in these patients. In this study, average levels of DPI, serum albumin, and serum creatinine were lower than those recommended by NKF guidelines [9]. Serum albumin is a useful marker of circulating protein, whereas serum creatinine is proportional to protein intake and the somatic mass [9, 12]. Combination of these parameters could indicate that PD patients might be at risk of protein-energy wasting (PEW) due to inadequate protein intake, loss of somatic mass, and low circulating protein. However, patients' clinical symptoms must be examined when low serum protein is present because decrease in serum protein concentration could be affected by non-nutritional factors including infection, inflammation, and hydration [13]. According to BMI, the patients were considered overweight and some were in obese state. The energy derived from dialysate glucose absorption seemed to play an important role in body fat accumulation [14]. The amount of fat mass was positively associated with the levels of inflammatory mediators, which could contribute to PEW [15].

The present study found that most of PD subjects had malnutrition with different degrees. The SGA is widely used in evaluating the nutritional status. The data from SGA indicated that the subjects who had poor scores were suffering from gastrointestinal problems and continued weight loss. However, SGA does not include the visceral protein levels in nutritional status determination [16]. Various factors contributed to malnutrition in PD patients including chronic kidney disease and modes of treatment. Both ESRD and PD factors could lead to poor nutritional status in PD patients and result in high mortality and morbidity rates [5, 17]. Inflammation is one of possible causes of malnutrition in the PD patients. Several inflammatory markers were found to be elevated in plasma and dialysate of the PD patients [18, 19]. This study focused on IL-6, and TNF-α because the negative association between these cytokines and the nutritional status has been established [4]. The presence of these cytokines possibly related to poor nutritional status in the PD patients. Levels of these cytokines in the present study were higher than in healthy controls, and were similar to those in dialysis patients in other studies [20, 21]. High levels of pro-inflammatory cytokines, when compared to those in healthy individuals may indicate that the PD patients in this study were suffering from inflammation, and therefore affecting the patients' nutritional status.

The presence of dialysate IL-6 in this study may reflect intra-peritoneal stimuli. IL-6 in peritoneal cavity can be produced by many cell types, such as macrophages and peritoneal mesothelial cells [22], and the high production indicated local inflammation. Sources of intra-peritoneal inflammation include bioincompatible dialysis solution, peritoneal dialysis catheters, and glucose degradation products [5, 23]. The lack of detectable dialysate TNF-α in the present study is generally consistent with previous studies of CAPD [24, 25]. However, some authors have reported high dialysate TNF-α levels in PD subjects [21, 26, 27]. Plasma and spent dialysate IL-6 concentrations which found in this study were in the same range of the concentrations reported from the previous studies [21, 26, 28, 29].

The lack of uniformity of reporting cytokine concentrations in PD patients may due to several factors. In this study, it was found that concurrent hypertension, PD treatment types, peritoneal transport characteristics, and adequacy of peritoneal dialysis were the factors that affected cytokine concentrations. Patients with hypertension had higher circulating IL-6 than patients without hypertension. IL-6 could potentially contribute to development of atherosclerosis through various mechanisms. Endothelial dysfunction, decreased adiponectin mRNA, and involvement in fibrous plaque formation have been proposed as IL-6-induced atherosclerosis mechanisms [4]. In addition, dialysate IL-6 concentration was higher in patients treated with CAPD than in those treated with APD. It is possible that APD could reduce intra-peritoneal inflammation. One study reported that the use of APD decreased the intra-abdominal pressure per volume of dialysate [30]. However, there was no difference between APD and CAPD in terms of reduced risk of peritonitis mortality [31].

The present study observed correlations between nutritional parameters and cytokine concentrations. It was found that plasma IL-6 concentrations were positively correlated with BMI and MAC. This finding agreed with Ekim et al. [32] who observed positive correlation between plasma levels of IL-6 and BMI in children undergoing CAPD, and Pecoits-Filho et al. [33] who demonstrated significant positive correlation between plasma IL-6 levels and BMI. In healthy volunteers, plasma IL-6 levels were positively correlated with BMI and percentage of body fat [34]. It seemed that circulating IL-6 was positively correlated with measures of adiposity. Studies suggested that 15-35% of systemic IL-6 may be released from adipose tissue because there are several cytokine encoding genes expressed in adipocytes [4, 34].

Negative correlations between plasma IL-6 and daily protein intake per body weight derived from a 3-day dietary record and DPI were found in this study. The finding agreed with previous study. Kalantar-Zadeh et al. [35] demonstrated that diminished appetite was associated with evidence for both higher concentration of IL-6 and low protein intake in hemodialysis subjects. IL-6 could conceivably lead to malnutrition either by increased protein catabolism or decreased appetite. However, the mechanism is still not clear. It was speculated that IL-6 may cause anorexia and eating behavior by increasing of leptin level [4]. This study also showed that the level of TNF-α in plasma was inversely correlated with DPI. One previous study demonstrated that PD patients with anorexia, nausea, or vomiting had higher plasma TNF-α levels than patients without these symptoms, suggesting that TNF-α decreased food intake by affecting the hunger center [36].

In conclusion, in the present study, inflammation was found in PD patients. Elevated plasma IL-6 and TNF-α levels indicated systemic inflammation and was possibly associated with malnourished state, whereas the presence of dialysate IL-6 indicated local peritoneal inflammation. Therefore, the markers of both inflammation and nutritional status were useful and should be routinely evaluated in PD patients.

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