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Original Article

The Relationship between Serum Procalcitonin and Dialysis Adequacy in Peritoneal Dialysis Patients

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Abstract

Background: To detect the serum procalcitonin (PCT) levels of peritoneal dialysis (PD) patients.

Methods: We analyzed the relationship between the PCT Level and dialysis adequacy. We studied 120 peritoneal dialysis patients without signs of infection in Affiliated Hangzhou First People's Hospital and 120 controls from Jan 2014 to Apr 2016. PCT and high sensitivity C-reactive protein (hs-CRP) were detected. 120 PD patients were divided into two groups according to the dialysis adequacy. A correlation analysis was processed between the PCT level and the total solute clearance (Kt/V). The value of PCT for identifying the dialysis adequacy in PD patients was assessed by ROC curve analysis.

Results: PCT level in serum of PD group (0.29±0.24 ng/ml) was higher than that of the control group (0.02±0.01 ng/ml) (P<0.01). Compared with the inadequate dialysis group (0.5±0.37 ng/ml), the PCT Level of the adequate dialysis group (0.23±0.15 ng/ml) was lower (P<0.01). There were negative correlations between PCT and Kt/v(r=-0.451), Prealbumin (PA) (r=-0.258), Glomerular Filtration Rate (eGFR; r=-0.280), while there was positive correlation between PCT and Hypersensitive c-reactive protein (r=0.458) (P<0.01). At a serum PCT cut-off value of 0.283 ng/ml, the sensitivity and specificity for identifying the dialysis adequacy in PD patients were 0.913 and 0.805 respectively. The serum levels of PCT in peritoneal dialysis patients were significantly higher than the levels in healthy controls.

Conclusion: The serum level of PCT can be used as an indirect maker to evaluate the adequacy of dialysis.

Keywords: Procalcitonin; Adequacy of dialysis; Microinflammation; Hypoproteinemia

Introduction

The number of patients with end-stage renal disease (ESRD) is increasing day by day with the development of social disease spectrum in recent years. Maintenance peritoneal dialysis (MPD), a renal substitute, is an effective treatment to stabilize the internal environment, treat symptoms and improve the quality of life of patients with end-stage kidney disease. Micro inflammation is prevalent in PD patients (1), closely related to the nutritional status and dialysis adequacy of patients. Therefore, how to identify infection early, reduce the occurrence and progression of chronic inflammation in dialysis patients, and improve the dialysis adequacy of dialysis patients is very important.

Serum procalcitonin (PCT) can not only reflect the presence of infection, but also reflect the non-infectious inflammatory reaction (2). The serum PCT Level of non-infected patients with chronic kidney disease (CKD), including dialysis, is significantly higher than that of healthy people (3-6). However, there are few reports of blood PCT Level in patients with PD.

Therefore, this study analyzed the correlation between serum PCT Level and microinflammation, malnutrition, dialysis adequacy in MPD patients without infection, and then explored its clinical value as an evaluation of PD adequacy.

Methods

Study subjects

This study is a retrospective, single-center clinical study. From Jan 2014 to Apr 2016, 120 patients with MPD in dialysis center of our hospital were taken as PD group for this study. There were 69 males and 51 females with an average age of (60.46±11.48) years. From the point of view of primary diseases, there were 65 cases of chronic glomerulonephritis, 18 cases of type 2 diabetes mellitus and 37 cases of hypertension. Inclusion criteria: the patients with stable condition, the patients MPD for 3 months or more, the patients treated with CAPD standard prescription, dialysate 2 L, 4 bags of dialysate per day, and abdominal cavity for 8-12 h at night. Peritoneal dialysis fluid is from Baxter Company. Exclusion criteria: 1) patients with acute cardiovascular and cerebrovascular complications, 2) patients with current or recent bleeding and infectious diseases, 3) patients with renal transplantation failure, 4) patients who used immunosuppressants or non-steroid in the past 3 months, 5) patients with malignant tumors, acute and chronic liver diseases, thyroid diseases, etc. At the same period, 120 healthy subjects in the physical examination center of our hospital were the controls, including 65 males and 55 females, with an average age of (50.45±11.91) years. There was no significant difference in age and sex between the PD group and the healthy control group (P>0.05).

Study Methods

Specimen Collection

PD Group: 5 ml of venous blood was collected on an empty stomach in the morning, and blood PCT, hs-CRP, hemoglobin (Hb), prealbumin (PA), serum creatinine (Scr) were detected.

Healthy Control Group: 5 ml of venous blood was collected on an empty stomach in the morning, and blood PCT and hs-CRP were detected.

Empirical Method

Determination of Inflammation Index: PCT, hs-CRP

Determination of PCT: The blood samples were collected in dry tube and centrifuged at 3000 r/min for 10 minutes. The serum was collected and stored at -80 ℃ for batch detection and analysis. PCT detection reagent (produced by German Roche Company) and electrochemical luminous method (the range detection of was 0.02~100 ng/mL) were used. The samples of dialysate were also collected in dry tube and centrifuged at 3000 r/min for 10 minutes. The serum was collected and stored at -80 ℃ for batch detection and analysis. PCT detection reagent (produced by German Roche Company) and electrochemical luminous method (the range detection of was 0.02~100 ng/mL) were used.

Determination of hs-CRP: The instrument is an IMMAGE800 automatic immune turbidity analyzer produced by BECKMAN CuLLTER Company. The immune rate scattering turbidimetric method was used.

Blood Biochemical and Nutritional Indexes

Serum prealbumin was determined by automatic biochemical analyzer Olympus.2700. Hemoglobin was detected by Perox staining method with automatic analyzer Advi.120.

Dialysis Adequacy Evaluation

Calculation of urea creatinine clearance rate (Kt/V)=(peritoneal urea clearance + residual renal urea clearance) / urea distribution volume × days of dialysis in a week. The average distribution volume of urea is calculated by the Watson formula.

nPCR=9.35×Gurea+0.294×VW/1.7×VW.

Glomerular Filtration Rate (GFR)

Serum creatinine was determined by automatic biochemical analyzer Olympus.2700, and GFR was calculated by simplified MDRD formula for China. GFR=175 × [creatinine mg/d1]$^{-1.234}$ × [age (years old)]$^{-0.179}$ × sex (M=1, F=0.79). Because the data collection creatine unit is umol/L, calculated by dividing the value by 88.4 to the value in mg/dl.

Statistical Method

SPSS ver.22.0 statistical software was used (Chicago, IL, USA). The measurement data were expressed by $\bar{X}\pm S$, and two independent samples t-test was used to compare the results between the two groups. The counting data were represented by frequency and composition ratio, and χ^2 test was used for the comparison between the two groups. The correlation of PCT Level with hs-CRP, Hb, PA, eGFR and Kt/V was analyzed by Spearman. The value of PCT Level in evaluating the adequacy of PD was analyzed by ROC curve. There was significant difference between the two groups when $P<0.05$.

Ethical considerations

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted following the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine (NO.: 2020-043-01). Informed consent was obtained from all the patients.

Results

Comparison of Differences of PCT Level between Two Groups

The PCT value in the PD group was 0.29±0.24 ng/ ml, which was significantly higher than that of the healthy control group (0.02±0.01ng/ml), it was statistically significant ($P<0.01$) (Table 1).

Table 1: PCT and hs-CRP in PD Group and Healthy Control Group (x±s)

Group	*n*	*PCT (ng/mL)*	*hs-CRP (mg/dL)*
PD Group	120	0.29±0.24[a]	0.84±1.21[a]
Healthy Control Group	120	0.02±0.01	0.17±0.12

General data and Level of PCT, hs-CRP, PA and Hb in Adequate Dialysis Group and Insufficient Dialysis Group

The general data of adequate dialysis group and insufficient dialysis group in PD group are shown in Table 2. There were no significant differences in sex, age, dialysis time and primary disease between the dialysis sufficient group and the insufficient dialysis group (all $P>0.05$). The PCT value of adequate dialysis group was 0.23±0.15 ng/ml, while the PCT value in insufficient dialysis group was 0.50±0.37 ng/ml. PCT level in insufficient dialysis group was significantly higher than that in adequate dialysis group ($P<0.01$). The hs-CRP value of adequate dialysis group was 0.62±1.06 mg/ml, while that in adequate group was

1.62±1.39 mg/ml. hs-CRP in insufficient dialysis group was significantly higher than that in adequate dialysis group (P<0.05). The PA value of adequate dialysis group was 0.33±0.17 g/l. The PCT value of insufficient dialysis group was 0.27±0.54 g/l. The level of PA in dialysis insufficiency group was significantly higher than that in dialysis sufficient group (P<0.05). There was no significant difference in Hb level between the adequate dialysis group (89.01±19.24 g/l) and insufficient dialysis group (85.91±20.19 g/l) (P>0.05) (Table 2).

Table 2: General data and Level of CRP, PA and Hb in Adequate Dialysis Group and Insufficient Dialysis Group (x±s)

Item	*Adequate Dialysis Group*	*Insufficient Dialysis Group*	*P-value*
Gender			
Male	41（59.4%）	32（62.7%）	＞0.05
Female	28（40.6%）	19（37.3%）	＞0.05
Age (Years Old)	59.18±12.46	60.12±15.13	＞0.05
Dialysis Time	47.45±10.12	52.16±13.56	＞0.05
Primary Disease [n(%)]			
Chronic Glomerulonephritis	26	25	＞0.05
Type 2 Diabetes	18	20	＞0.05
Hypertension	31	30	＞0.05
PCT(ng/mL)	0.23±0.15	0.50±0.37	<0.01
hs-CRP(mg/dL)	0.62±1.06	1.62±1.39	<0.01
PA(g/L)	0.33±0.17	0.27±0.54	<0.01
Hb(g/L)	89.01±19.24	85.91±20.19	0.5

Analysis on Correlation between PCT and Inflammatory Index (hs-CRP), Nutritional Index (PA, Hb), GFR, Dialysis Adequacy (KT/V)

By Spearman-related analysis, the PCT in PD group was positively correlated with hs-CRP, and the correlation coefficient was 0.458 (P<0.01). It was negatively correlated with PA, eGFR and KT/V, and the correlation coefficients were -0.258, -0.280 and 0.451, respectively (P<0.01). It does not correlate with Hb, and the correlation coefficient was -0.166 (P>0.05) (Table 3). The linear relationship between fitting PCT and the above indexes is detailed in Figs. 1-5, respectively.

Table 3: Correlation between PCT and Inflammatory Index, Nutritional Index, eGFR, Dialysis Adequacy in PD Group

	PCT (ng/mL)	
	Correlation Coefficent (r)	*P*-value
hs-CRP(mg/dl)	0.458	<0.01
Prealbumin (g/L)	-0.258	<0.01
Hemoglobin（g/L）	-0.166	0.090
eGFR(ml/min)	-0.280	<0.01
Kt/V	-0.451	<0.01

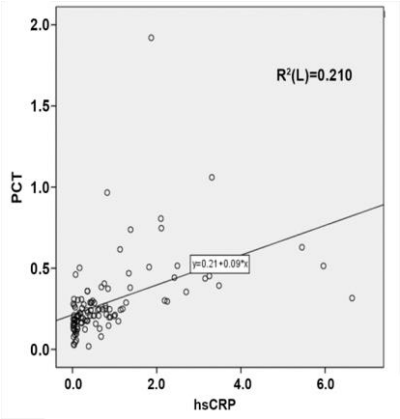

Fig. 1: Correlation between PCT and hs-CRP

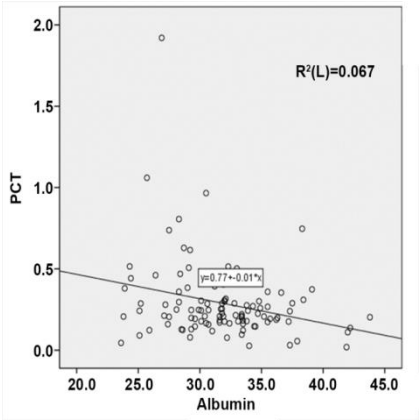

Fig. 2: Correlation between PCT and Prealbumin

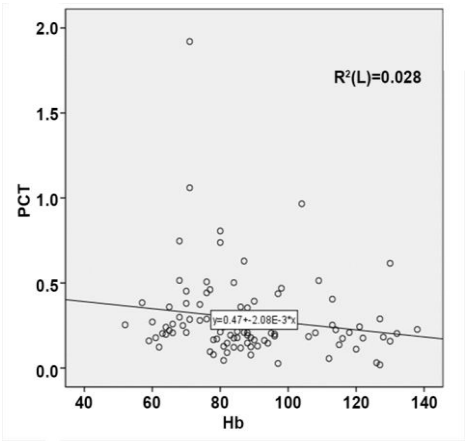

Fig. 3: Correlation between PCT and Hemoglobin

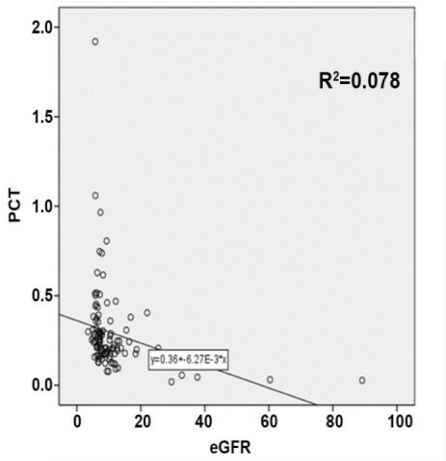

Fig. 4: Correlation between PCT and eGFR

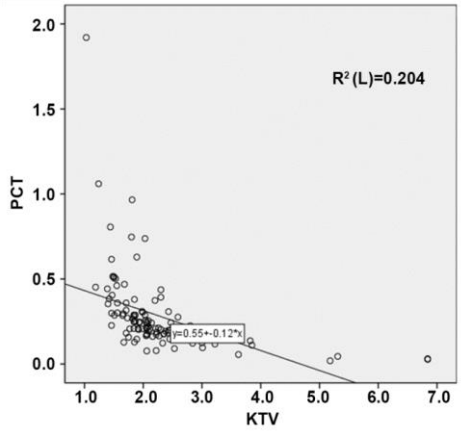

Fig. 5: Correlation between PCT and KT/v

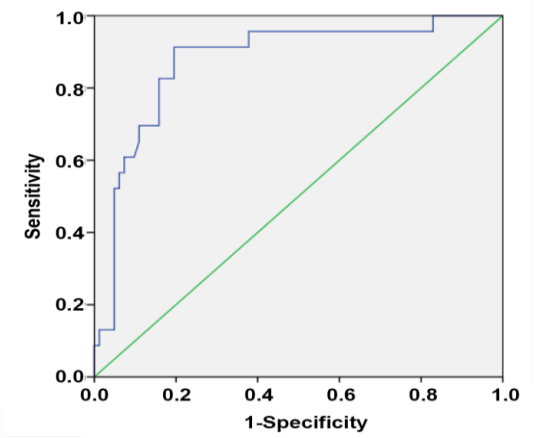

Fig. 6: ROC Curve of PCT on Dialysis Adequacy in PD Group

Analysis on Characteristics of ROC Curve of Evaluation of PD adequacy by Serum PCT

To further evaluate the evaluation value of PCT for dialysis adequacy, the ROC curve of PCT on dialysis adequacy was drawn (Fig. 6).

According to the curve analysis, the area under the ROC curve of PCT in PD group was 0.875 (95% CI 0.792~0.958). The sensitivity of serum PCT was 91.3% when the cut-off value was 0.283 ng/ml, and the specificity was 80.5% (Table 4).

Table 4: Analysis Results of ROC Curve of PCT in PD Group

Group	*AUC*	*cut-off value*	*Sensibility*	*Specificity*	*P-value*	*r-value*
PD Group	0.875	0.283	0.913	0.805	<0.01	0.718

Note: Correct diagnostic index (r) = Sensibility + Specificity - 1

Discussion

Procalcitonin (PCT) is the first protein detected in the serum of patients with sepsis in the 1990s. It is a biological index of systemic bacterial infection (7,8). Under physiological condition, PCT is mainly produced by thyroid C cells, which is very stable in vivo, does not release into peripheral blood, and will not be degraded into calcitonin with hormone activity. In healthy people, PCT Level is very low, usually 0.1~0.5 ng/L. In the case of infection, PCT appeared and increased earlier than CRP, IL-6 and other acute proteins and inflammatory factors, and the half-life was shorter, so PCT had higher sensitivity and specificity. Animal studies have found that injection of IL-6 and TNF-α in a rat model of sepsis can cause large-scale release and increase of PCT, and PCT itself has no significant effect on the increase of cytokines, PCT can be a secondary inflammatory factor and amplify the inflammatory effect (8). At present, there are few studies on the clearance of PCT. In patients with chronic kidney disease, PCT level has increased, but not significantly, which indicates that in the clearance link of PCT, the kidney is not its main metabolic pathway. In this part of patients, PCT as an infectious indicator still has guiding significance (5,9).
At present, serum PCT level is increased in CKD patients who do not receive dialysis and in hemodialyzed patients even in the absence of infection (3,10). Our study found that the serum PCT level was 0.29±0.24 ng/mL, which was significantly higher than that in healthy people, even if there was no obvious sign of infection in patients with MPD. At the same time, PCT in patients with PD was positively correlated with hs-CRP (r=0.458), and negatively correlated with residual kidney function (eGFR) (r=-0.280). PCT level in PD patients is higher than that in healthy controls, but lower than that in hemodialysis patients (11, 12). At the same time, PCT level is inversely proportional to GFR and residual urine volume in end-stage patients. This study also found that PCT level was negatively correlated with eGFR, which indicated that even if PCT was not mainly dependent on renal metabolism, the increase of PCT Level was still related to the decreased GFR in patients with PD. In addition, the micro inflammatory state of patients with chronic kidney disease will lead to the increase of PCT production in peripheral blood monocytes. While for PD patients, due to the retention of various inflammatory metabolites in the body, the long-term stimulation of dialysate to the human body, the weakening of intestinal barrier effect lead to the increase of endotoxin uptake and the irregular operation of peritoneal dialysis. The micro inflammatory response is more obvious than that of other patients, and monocytes produce more PCT, resulting in high serum PCT level in patients with PD. This study also found that PCT

level in patients with PD was negatively correlated with traditional inflammatory indexes. Therefore, we speculate that the increased level of PCT in peritoneal dialysis patients is related to the decreased residual renal function and persistent microinflammation. PCT can be used as an indicator of microinflammatory status in maintenance peritoneal dialysis patients.

For patients with long-term maintenance dialysis, dialysis adequacy is an important index to measure dialysis level, and it is a necessary guarantee to improve the disorder of internal environment and quality of life of patients. Dialysis adequacy can affect the long-term survival rate of patients and predict the poor prognosis of patients. Due to the increased incidence of hypoproteinemia and cardiovascular and cerebrovascular events in patients with inflammatory status, it also has a certain impact on dialysis sufficiency, and PCT can be used as a sensitive indicator of inflammation. Therefore, correlation analysis was conducted on dialysis sufficiency and related nutritional indicators of PCT peritoneal dialysis patients. PCT in PD patients was negatively correlated with Kt/v, serum prealbumin and GFR, but not significantly correlated with hemoglobin. This negative correlation indicates that the rise of PCT indicates the aggravation of malnutrition; on the other hand, PCT reflects the sufficiency of dialysis in patients to some extent. In addition, according to the adequacy of dialysis, peritoneal dialysis patients were divided into the adequate dialysis group (Kt/v≥1.7) and the inadequate dialysis group (Kt/v<1.7). The PCT level of the inadequate dialysis group was significantly higher than that of the adequate dialysis group. The ROC curve analysis of PCT on dialysis sufficiency showed that the area under the ROC curve was 0.875 (95% CI 0.792 ~ 0.958). When the cut-off value was 0.283 ng/ml, the sensitivity and specificity of serum PCT were 91.3% and 80.5% respectively. This further suggests that elevated PCT predicts poor dialysis adequacy. Therefore, we believe that because of the convenience of PCT test, it can be used as an indirect indicator of dialysis adequacy in dialysis patients.

Conclusion

PCT level in peritoneal dialysis patients is significantly higher than that in healthy people even under non-infectious conditions. PCT can be used as an indicator of micro inflammatory status in peritoneal dialysis patients, indirectly evaluating the nutritional status of dialysis patients and the adequacy of dialysis.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Ortega O, Rodriguez I, Gallar P, et al (2002). Significance of high C-reactive protein levels

in pre-dialysis patients. *Nephrol Dial Transplant,* 17 (6): 1105-9.
2. Pipili C, Grapsa E, Tripodaki ES, et al (2015). Changes in skeletal muscle microcirculation after a hemodialysis session correlates with adequacy of dialysis. *Int J Nephrol Renovasc Dis,* 8: 59-64.
3. Trimarchi H, Dicugno M, Muryan A, et al (2013). Pro-calcitonin and inflammation in chronic hemodialysis. *Medicina (B Aires),* 73 (5): 411-6.
4. Dahaba AA, Rehak PH, List WF (2003). Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. *Intensive Care Med,* 29 (4): 579-83.
5. Herget-Rosenthal S, Klein T, Marggraf G, et al (2005). Modulation and source of procalcitonin in reduced renal function and renal replacement therapy. *Scand J Immunol,* 61 (2): 180-6.
6. Contou D, D'Ythurbide G, Messika J, et al (2014). Description and predictive factors of infection in patients with chronic kidney disease admitted to the critical care unit. *J Infect,* 68 (2): 105-15.
7. Wang X, Sun Y, Shao X (2019). Predictive value of procalcitonin for infection of patients with type-2 diabetes mellitus. *Exp Ther Med,* 18 (1): 722-8.
8. Fu Y, Chen J, Cai B, et al (2012). The use of PCT, CRP, IL-6 and SAA in critically ill patients for an early distinction between candidemia and Gram positive/negative bacteremia. *J Infect,* 64 (4): 438-40.
9. Meisner M, Lohs T, Huettemann E, et al (2001). The plasma elimination rate and urinary secretion of procalcitonin in patients with normal and impaired renal function. *Eur J Anaesthesiol,* 18 (2): 79-87.
10. Level C, Chauveau P, Delmas Y, et al (2001). Procalcitonin: a new marker of inflammation in haemodialysis patients? *Nephrol Dial Transplant,* 16 (5): 980-6.
11. Steinbach G, Bölke E, Grünert A, et al (2004). Procalcitonin in patients with acute and chronic renal insufficiency. *Wien Klin Wochenschr,* 116 (24): 849-53.
12. Boonyarittipong M, Kurathong S, Trakarnvanich T (2019). Interleukin-6, procalcitonin, and vascular endothelial growth factor in plasma and dialysate correlate with dialysis adequacy in continuous ambulatory peritoneal dialysis patients. *Clin Nephrol,* 92 (5): 273-5.