Diagnostic Values of Serum Procalcitonin in Kidney Diseases

Masoumeh Mohkam,¹* Farshid Kompani,² Alireza Ghafari³

1 Pediatric Nephrology Research Center Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2 Pediatric Nephrology Department. Ahvaz University of Medical Sciences, Ahvaz, Iran.
3Technical Deputy of Khanevade Hospital, Tehran, Iran.

*Corresponding Author
Masoumeh Mohkam, Shariati Ave, Mofid Children’s Hospital, Tehran, Iran
Email: mohkam@pirc.ir
Tel: +98(21)22227033

Many clinical studies have confirmed biomarkers like procalcitonin (PCT) as a specific inflammatory marker in sepsis and bacterial infections. It is believed that PCT level is increased in various noninfectious conditions such as acute pancreatitis, major surgery, trauma and active autoimmune disease. In recent studies increased levels of serum PCT was distinguished in several kidney diseases like pyelonephritis, vesicoureteral reflux, kidney transplantation and hemodialysis. The aim of this review is to describe usefulness of PCT and practical aspect of this biomarker in nephrology field.

Keywords: Procalcitonin; Biomarker; Pyelonephritis; Kidney Diseases; Kidney Transplantation; Vesico-Ureteral reflux.

Introduction
Procalcitonin (PCT) is a propeptide (13-kDa protein and 116 amino acid peptide) of calcitonin (Fig.1). PCT was first described by Assicot et al as a biologic marker of bacterial invasion in humans [1]. In healthy subjects, this protein is produced in the C-cells of the thyroid gland and pulmonary neuroendocrine cells. It is well established that during a widespread bacterial infection, PCT is produced by the monocyte-macrophage system. Serum PCT level below 0.1 ng/ml is commonly detected in healthy normal subjects.

PCT as an Inflammatory Marker
Many clinical studies have confirmed PCT as a specific inflammatory marker in sepsis, bacterial and fungal infections and as a good predictor of disease severity [2-7]. In microbial infections serum levels of procalcitonin increase several fold to several thousand-fold, and this increase often has a positive correlation with the severity of the infection and with mortality [2, 8, 9]. Simon et al performed a meta-analysis to evaluate the accuracy of PCT and C-reactive protein levels for the diagnosis of bacterial infection in hospitalized patients. They retrieved 110 publications in which PCT and/or CRP levels were determined in hospitalized patients with bacterial infections. These researches included 46 neonates, 638 children, and 702 adults in different wards. The results derived from the meta-analysis were shown that PCT was more sensitive than CRP level for differentiating bacterial from noninfective causes of inflammation. In this study the sensitivity for differentiating bacterial from viral infections was also higher for PCT. Pooled sensitivity for PCT was 88% compared with 75% for CRP. Pooled specificity for PCT was also higher than for CRP (81% vs. 67%). There was a statistically significant difference between the sensitivities and the specificities (P < 0.05 and P < 0.05). The results of the meta-analysis showed that the diagnostic accuracy of PCT was higher than that of CRP among patients hospitalized for...
suspected bacterial infections [10]. The mechanism of PCT production after inflammation and its role are still not completely known. It seems that PCT is produced by the liver and mononuclear cells of the peripheral blood. It is believed that PCT is modulated by lipopolysaccharides and sepsis-related cytokines [11-12]. It is reported that elevation of PCT may be harmful and it increases mortality in patients suffering from sepsis. The researchers demonstrated that immunoneutralization of PCT improved survival of sepsis models in animal studies [13].

**Figure 1.** Schematic illustration of Calcitonin and its precursors. PAM: Peptilyl Glycine amidating monooxygenase (Thyroidal C-cell enzyme)

### PCT in Noninfectious Diseases

Although the exact functions of PCT have not been determined yet, it was recently proposed that PCT is not only a marker but also a proinflammatory mediator with deleterious and harmful effects [14-17]. It is believed that the level of PCT is increased in various noninfectious, inflammatory conditions such as acute pancreatitis [18], major surgery [19], trauma [20], active autoimmune disease [21], and systemic inflammatory response syndrome [22-23].

### PCT in Acute Pyelonephritis

In most recent studies the researchers evaluated the relationship between serum PCT and pyelonephritis, however our knowledge of urinary levels of PCT is very limited. In 1998 Benador et al evaluated serum PCT levels in 80 pyelonephritic children. They assessed renal involvement by \(^{99mTc}\)-DMSA scintigraphy in the first 5 days after admission and repeated the DMSA examination at least 3 months later. They concluded that serum PCT levels were increased significantly in children with febrile UTI and a positive DMSA scintigraphy. They recommended Serum PCT for prediction of pyelonephritic patients at risk of severe renal lesions [24]. In a prospective study Gervaix et al measured serum PCT in children admitted to the emergency room with urinary tract infection and assessed renal parenchymal involvement by a \(^{99mTc}\)-DMSA scintigraphy in the acute phase of infection. They concluded that a positive PCT value predicted renal involvement in 87 to 92% of children with febrile UTI and proposed a rapid determination of procalcitonin concentration for the management of children with febrile UTI in the emergency room [25]. After that many researchers demonstrated serum procalcitonin as a good predictor of acute pyelonephritis in children [26-27], they also reported a significant correlation between serum levels of PCT and the presence of renal scars in children with acute pyelonephritis [28-29]. In a meta analysis Mantadakis et al evaluated 10 studies and a total of 627 pyelonephritic patients and concluded that in pediatric patients with confirmed UTI, a serum PCT value >0.5 ng/ml predicts the presence of renal parenchymal involvement [30].

### PCT in Vesicoureteral Reflux

In addition the importance of serum PCT was evaluated in vesicoureteral reflux (VUR) and it was demonstrated that high levels of PCT (≥0.5 ng/ml) was associated with VUR [31-32]. They also showed that Strength of the relationship between PCT level and the severity of VUR increased with the grade of VUR (P = 10^{-5}). Leroy reported that the sensitivity of PCT was 75% (95% CI, 66 to 83) for all grades of VUR and 100% (95% CI, 81 to 100) for grades 4 and 5 [31]. They recommended measuring PCT level as a strong, independent and now reliable predictor of VUR that can be used to identify high-risk patients. Determination of PCT level can avoid one third of the unnecessary cystourethrography in pediatric patients with a first attack of pyelonephritis.

### PCT in Chronic Kidney Diseases

Moderately increased PCT was demonstrated in chronic kidney diseases (CKD) patients in the absence of infections [33-35]. It is believed that
the inflammation observed in earlier stages of CKD may exert harmful effects [36-38]. In fact the origin of PCT and its underlying factors remain to be elucidated in CKD patients. It is hypothesized that in CKD and dialysis patients, PCT may also originate from peripheral blood mononuclear cells (PBMC) [39-42].

**PCT in Dialysis**

Recent studies reported serum PCT as an accurate indicator of severe infection and sepsis in patients undergoing hemodialysis (HD) [43-45]. Herget-Rosenthal et al evaluated serum levels of PCT in 281 CKD, 31 PD, and 65 HD patients and 37 controls, and correlated it with being on PD or HD, C-reactive protein (CRP) level, the presence of cardiovascular disease (CVD) and the CKD stage. They also measured the PCT release by PBMC in their study groups. They reported that PCT increased in CKD patients, oliguric situations and patients undergoing PD and HD. They also demonstrated elevation of PCT in patients with CVD and high levels of CRP. In this study PCT release from PBMC significantly increased in advanced CKD, PD and HD patients and also PCT release from PBMC correlated closely with the corresponding serum PCT values ($r = 0.76$, $P < 0.001$). They concluded that in the absence of infection, PCT may increase due to decreased GFR and increased synthesis by PBMC. Furthermore, serum PCT could be a marker of low-grade inflammation and CVD, which substantially increase the rate of mortality in CKD and dialysis patients [46]. Low-grade inflammation is characteristic of patients undergoing HD or PD and promotes atherosclerosis and CVD thus contributing substantially to the high morbidity and mortality in these groups [47-48].

Based on Chauveau study, the concomitant presence of a high level of PCT and CRP was associated with a worsened nutritional status in HD patients [49-50], but they detected no correlation between PCT level and the rate of mortality in this group [50]. Recent data support that PCT is a more precise marker than other traditional tests to evaluate micro-inflammation and biocompatibility in patients undergoing HD [51]. Furthermore serum PCT would be an accurate indicator of severe infection in patients receiving HD. It should be noted that high-flux membranes substantially decrease the serum levels of PCT, so when utilizing high flux membranes, serum PCT levels should be measured prior to the start of HD [52]. Dahaba et al in a Prospective observational consecutive clinical study established that uremia per se and not the dialysis process is the origin of PCT elevation. They showed that serum PCT levels declined with successive hemodialysis [53]. Lorton et al showed that serum levels of PCT 15 and 60 minutes after the start of dialysis remained unchanged in comparison with those at the end of the HD session. Their data suggested that accumulation of PCT in serum between HD sessions rather than HD per se may be responsible for the increased levels of PCT at baseline. It should be considered that increased serum levels of PCT are presumably due to reduced renal function and uremia [54]. On the contrary Sitter et al showed that the PCT levels are not significantly affected by loss of renal function, autoimmune disorders or immunosuppressive drugs. They concluded that significantly elevated PCT levels in serum offer good sensitivity and specificity for the early diagnosis of systemic bacterial infection in CKD and HD patients [55]. Kalocheretis et al determined that the strong correlation of B2-Microglobulin with PCT in the serum of chronic hemodialysis patients established a role for infections in the dialysis-related amyloidosis [56].

**PCT in Kidney Transplantation**

PCT was established as a postoperative infection marker in organ transplantation. Eberhard et al tested serum levels of PCT for its utility in detecting bacterial infections and acute rejection during the first 6 wk after kidney transplantation. They noticed that PCT rose postoperatively to peak levels on the first days of kidney transplantation and mostly declined to the normal value within 1 wk. The authors concluded that serum PCT was not influenced by acute kidney graft rejection but served as a specific indicator of systemic bacterial infection [57]. Jarešová et al also measured PCT concentrations in 419 serum samples of heart and kidney transplant patients. In their study PCT concentrations dramatically increased 100-300 fold in severe bacterial infections and appropriate response to antibiotic therapy was associated with a decline in PCT levels. They noticed that either acute rejection episodes or cytomegalovirus infections did not significantly increase the serum levels of PCT. They concluded that serum levels of PCT can be used as a sensitive marker to differentiate systemic bacterial infections from other complications in organ transplant patients [58]. Sabat et al determined the value of serum PCT in
infection-free kidney transplant patients receiving pan-T-cell antibody therapy. They surprisingly found out a 1000 fold increase in PCT plasma concentrations which is comparable to that seen in severe sepsis. In this study the PCT plasma levels returned to normal values after the first day of therapy independently of further antibody administration. They recommended that PCT monitoring for evaluation of infections diseases in kidney transplant recipients must be very carefully interpreted during pan-T-cell antibody therapy [59]. In this regard Jung et al investigated the role of PCT and myeloid-related proteins 8 and 14 (MRP 8/14) in kidney transplant recipients as prognostic or diagnostic markers for allograft rejection and bacterial infections. They suggested that the MRP 8/14 and PCT parameters are not valid prognostic markers for allograft rejection. The results of this study indicated a significant increase in serum MRP 8/14 concentration in infection free acute rejections. They showed that non-rejection patients with infections only had elevation in the PCT serum concentrations. They proposed the combined use of MRP 8/14 and PCT concentrations for differentiation between allograft rejection and the other inflammatory processes, such as infection [60].

Conclusion
We concluded that serum procalcitonin level is a valuable method to detect bacterial infections in different kidney diseases and significantly elevated PCT levels in serum offer good sensitivity and specificity for the early diagnosis of systemic bacterial infection in CKD and hemodialysis patients and in kidney transplant recipients.

Conflict of Interest
None declared

Financial Support
None declared

References
21. Eberhard OK, Haultitz M, Brunkhorst FM, Klim V,
Serum Procalcitonin in Kidney Diseases – Mohkam M et al


