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Original Article

The Predictive Value of Serum Procalcitonin Levels in Adult Patients with Active Pulmonary Tuberculosis

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SUMMARY: The aim of our prospective study was to evaluate the predictive value of serum procalcitonin (PCT) level in comparison with C-reactive protein level and erythrocyte sedimentation rate for the diagnosis of pulmonary tuberculosis (PTB) on admission and 6 months after the administration of anti-tuberculous chemotherapy (ATCT). Seventy-five adult male patients with active PTB who were mycobacteriologically diagnosed (smear and culture positivity) were examined in this study. As a control group, 75 healthy adult males were enrolled. The measured serum PCT levels were within the normal range both in healthy individuals and in patients 6 months after ATCT. Serum PCT levels had been slightly high on admission in patients with PTB in comparison with controls ($P = 0.01$) and patients who had ATCT ($P = 0.001$), and this difference was statistically significant, but the PCT levels of most cases with PTB (58.7%) were below the usual cut-off level (0.5 ng/mL). We conclude from this study that the serum PCT level was not a reliable indicator in the diagnosis of active PTB because of its low sensitivity (41.3%), and in most cases it was not capable of overcoming the cut-off level even if statistically meaningful results were obtained. The PCT test for the presumptive diagnosis of PTB cannot be substituted for microbiological, epidemiological, clinical and radiological data.

INTRODUCTION

Procalcitonin (PCT) is considered to be an acute phase protein, which consists of 116 amino acids with a molecular weight of 13 kDa (1-5). PCT is a propeptide of calcitonin, which is normally produced by C-cells of the thyroid gland (6). According to a very recent in vivo and in vitro study, the major source of PCT seems to be the liver (5).

Series of chemokines and cytokines, such as interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β were produced in patients with pulmonary tuberculosis (PTB) (7-9). Significant levels of lipoarabinomannan (LAM) are also detectable in the systemic circulation of patients with clinical TB (10). LAM is a major lipopolysaccharide (LPS) that dominates the mycobacterial cell wall and is a key molecule in eliciting cytokine secretion by macrophages, which is thought to be a major stimulus of TNF-α release in patients infected with *Mycobacterium tuberculosis* (10,11). Pro-inflammatory cytokines (TNF-α, IL-1, IL-2 and IL-6) and bacterial LPS have been shown to increase the production of PCT in the systemic circulation (12-14). However it is not known how *M. tuberculosis* infections affect PCT production in adult patients with active PTB. Since these factors are involved in PTB as well, we extrapolated these data for PTB patients. It is expected that pro-inflammatory cytokines and LAM, which play important roles in PTB pathogenesis, may also increase PCT levels (15-18).

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In this study we evaluated the predictive value of serum PCT level in comparison with C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) for the diagnosis of active PTB on admission and 6 months after antituberculous chemotherapy (ATCT) in patients admitted to the hospital. To our knowledge, this is the first study to evaluate serum PCT levels in a large number of PTB patients (both on admission and 6 months after ATCT) in comparison with a control group.

MATERIALS AND METHODS

Patients and controls: Seventy-five adult male patients, aged 19-80 (mean age 23.1 ± 7.2) years, who had been mycobacteriologically diagnosed (smear and culture positivity) with active PTB were examined in this study. All of our patients were male, because our study was performed in a military hospital. These patients had no other severe illnesses. Physical and radiological examinations revealed that the severity of the illnesses of PTB patients varied on admission. As a control group, 75 healthy adult males (18-56 years; mean age 23.3 ± 5.7) with no physiological complaints were enrolled in the study. Only male individuals were selected for the control group so as to correspond to the patient group in terms of gender. Since PCT, CRP and ESR are routine tests for patients suspected of infection in our hospital, we just collected the data produced during routine medical practices. Informed consent was obtained from the patients and controls.

Clinical specimens: In our study, the clinical specimens obtained from patients suspected to have PTB were sputum samples and other respiratory secretions (bronchoalveolar lavage, transtracheal aspiration, gastric lavage). The clinical specimens were decontaminated and homogenized by a sodium hydroxide and N-acetyl-L-cysteine procedure recommended by the Centers for Disease Control and Prevention

Table 1. Comparison of age and serum procalcitonin (PCT) levels of the different groups

	Groups			*t*	*P*
	Pulmonary Tuberculosis		Controls		
	On admission	After therapy			
Number of cases	75		75	–	–
Age in years (mean ± SD) (range)	23.1 ± 7.2 (19-80)		23.3 ± 5.7 (18-56)	–0.15[1)]	0.881
PCT in ng/mL (mean ± SD) (range)	0.47 ± 0.28 (0.02-1.09)	0.15 ± 0.09 (0.03-0.43)	0.15 ± 0.11 (0.02-0.47)	[2)]	
CRP in mg/L (mean ± SD) (range)	36.13 ± 38.37 (5.0-185.5)	5.40 ± 4.39 (2.4-24.2)	–	7.27[3)]	0.001
ESR in mm/first hour (mean ± SD) (range)	37.41 ± 26.21 (4-115)	9.68 ± 8.64 (2-34)	–	11.34[3)]	0.001

[1)]: Statistical analyses were done by student *t* test.
[2)]: Statistical analyses were shown in Table 2.
[3)]: Statistical analyses were done by paired *t* test.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

(Atlanta, Ga., USA). Each specimen was concentrated by refrigerated centrifugation at 3,000 × g for 15-20 min after phosphate buffer was added (pH 6.8). Smears were prepared from the sedimented specimens for Ehrlich-Ziehl-Neelsen (EZN) staining. The remaining sediment was used for culture by the BACTEC 460TB system (Becton Dickinson Diagnostic Instruments, Sparks, Md., USA) and conventional Lowenstein Jensen medium (Salubris Inc., Istanbul, Turkey) and incubated at 37°C. BACTEC 12B vials were screened three times per week for the first 3 weeks, and weekly for the next 3 weeks using the BACTEC 460 instrument. Any vial with a growth index (GI) ≥10 was considered to be positive. At the end of the 6 weeks, vials with GI <10 were considered to be negative. Smears from both specimens and growth-positive 12B vials were stained by the EZN method and examined microscopically in order to confirm the presence of acid-fast bacilli (AFB). Differentiation of the *M. tuberculosis* complex (MTC) and non-tuberculous mycobacteria was achieved by selective inhibition of the MTC in the presence of 5 μl/mL of p-nitro-α-acetyl-amino-β-hydroxypropiophenone (NAP) according to the BACTEC manual. At the end of the sixth month following the initiation of therapy, the microscopic examination and cultures were repeated.

PCT, CRP and ESR analyses: Venous blood samples were drawn from the patients with PTB both on admission and 6 months after ATCT, and also were drawn from the control group. The first measurements of PCT in patients were performed on admission to the hospital. During this measurement, ATCT was not administered. Serum samples were kept at −20°C until the day of the PCT and CRP tests. The CRP and ESR tests of the control group were not done. Serum PCT and CRP levels were tested by an immunoluminometric assay (LUMItest PCT; B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany) using the Lumat LB 9507 analyzer (EG & G, Berthold, Germany) and by a turbidimetric assay (C-reactive Protein Turbidimetry Latex; BioSystem, Barcelona, Spain) using the BTS Analyzer (BioSystem), respectively. The ESR was detected in anticoagulated blood by the conventional Westergren method. The upper limits of normal PCT, CRP and ESR were 0.5 ng/mL, 6 mg/L and 0-10 mm/first hour, respectively. All of the tests were performed in duplicate.

Statistical analysis: Mean PCT, CRP and ESR levels of patients with PTB (on admission and 6 months after ATCT) were compared by student *t* and paired *t* tests. In addition, the correlation between PCT, CRP and ESR levels was done by Pearson correlation analysis. SPSS for Windows 10.0 was used for the analysis of the data. *P* values <0.05 were considered to be statistically significant.

RESULTS

Comparisons of the ages and serum PCT levels of the different groups are shown in Table 1. There was no statistical difference ($P = 0.881$) between the age groups. Statistical analyses of serum PCT levels of the different groups are presented in Table 2. Serum PCT levels were found to be significantly higher in patients with PTB (on admission) compared with the ATCT ($P = 0.001$) and control ($P = 0.01$) groups, but the PCT levels of most cases with PTB (58.7%) were below the usual cut-off level (0.5 ng/mL). Whereas the increase in serum PCT levels was not statistically significant in the ATCT group compared to the control group ($P = 0.9$). On admission, 41.3% (31 of 75) of the PTB patients had slightly elevated (0.5-2 ng/mL) serum PCT levels. The highest PCT level measured was 1.09 ng/mL. Serum PCT levels over 1.0 ng/mL were detected in only 5 (6.7% of total) patients on admission. The CRP ($P = 0.001$) and ESR ($P = 0.001$) levels were also found to be significant in patients with PTB (on admission) compared with the ATCT group (Table 1).

Results for the cut-off values of 0.5, 0.2 and 0.1 ng/mL, the sensitivity, specificity, positive predictive values and negative predictive values of serum PCT levels in patients with PTB on admission are shown in Table 3. At the same time,

Table 2. Statistical analyses of serum procalcitonin levels of the patients with pulmonary tuberculosis (PTB) and control group

	PTB (after therapy)		Controls	
PTB (on admission)	$t = 10.04$	$P = 0.001$	$t = 9.145$	$P = 0.01$
PTB (after therapy)	–		$t = 0.12$	$P = 0.9$

Statistical analyses were done by student *t* test.

Table 3. The sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values of PCT levels at different cut-off values in patients with pulmonary tuberculosis (on admission)

Cut-off values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.5 ng/mL	41.3	100	100	63.0
0.2 ng/mL	80.0	69.3	72.3	77.6
0.1 ng/mL	89.3	46.7	62.6	81.4

Table 4. The correlations between PCT, CRP and ESR levels of patients with pulmonary tuberculosis on admission and after anti-tuberculous chemotherapy

		PCT		CRP	
		On admission	After therapy	On admission	After therapy
ESR	On admission	r =0.06 , P = 0.62	–	r = 0.26 , P=0.026	–
	After therapy	–	r = −0.16 , P = 0.17	–	r = 0.07 , P = 0.57
CRP	On admission	r = −0.05 , P = 0.64	–	–	–
	After therapy	–	r =0.12 , P = 0.28	–	–

Correlation analyses were done by Pearson correlation test.
Abbreviations are in Table 1.

the correlations between PCT, CRP and ESR levels of the patients with PTB on admission and after ATCT were investigated in this study (Table 4). We did not detect any correlations between PCT and CRP levels, and PCT and ESR levels on admission. However, there was a positive correlation between CRP and ESR levels (r = 0.26; P = 0.026). There was no correlation among PCT, CRP and ESR levels obtained after ATCT. After 6 months of ATCT, the new physical and radiological examinations and microbiological tests of our patients showed that all the patients had fully recovered. We did not see any relapse or ATCT failure in our patients with PTB.

DISCUSSION

PCT has recently been proposed as a marker of bacterial infection and sepsis. PCT supports early diagnosis and clinical decision-making which could direct an effective therapy in a timely manner. PCT levels increase with the increasing severity of the inflammatory response to infection and may help in assessing the severity of infection, the prognosis of disease, and the response to therapeutic measures (1-6,12,13).

Serum PCT levels measured by LUMItest PCT are classified as normal (<0.5 ng/mL), slightly elevated (0.5 - 2 ng/mL), moderately elevated (2 - 5 ng/mL) and highly elevated (>5 ng/mL) (19). Serum PCT levels are detected as <0.5 ng/mL in healthy subjects and subjects with chronic inflammatory processes, autoimmune diseases, viral infections and mild to moderate localized bacterial infections. They are found to be between 0.5 - 2 ng/mL in systemic inflammatory response syndrome, multiple trauma and burns. However, they are determined to be >2 ng/mL (often 10 - 100) in severe bacterial infections, sepsis and multiple organ failures (1,4,6,13,14,20).

There is insufficient information concerning the activity of PCT in chronic infectious diseases such as active PTB. There are limited studies on the evaluation of PCT as a predictive marker of PTB and as a follow-up tool (15-18,21). However, these studies involved limited numbers of patients and no control groups or control groups with limited numbers of individuals. Zarka et al. (15) evaluated 49 adult patients with respiratory tract infections including PTB caused by different etiologies. Only 20 patients were found to have elevated serum PCT levels higher than 0.5 ng/mL. However, the serum PCT levels were normal in patients with PTB on admission. They claimed that PCT seems to be an early marker of the evolution of respiratory tract infections, but it does not help in the diagnosis of PTB. Lawn et al. (16) also reported elevated serum PCT levels in 2 out of 20 adult PTB patients on admission. In these 2 patients, serum PCT levels were found to be slightly elevated at the time of diagnosis, namely 1.0 and 1.6 ng/mL, and returned to normal by the end of the first month of ATCT. On the other hand, Polzin et al. (17) investigated the diagnostic significance of serum PCT and CRP levels in lower respiratory tract infections (25 patients with hospital-acquired pneumonia [HAP], 26 with community-acquired pneumonia [CAP], 26 with acute exacerbation of chronic bronchitis [AECB]) (n = 77) and PTB (n = 27). The median PCT levels in HAP, CAP, AECB and PTB were not elevated in relation to the cut-off level of 0.5 ng/mL. The report indicates that acute lower respiratory infections, such as HAP (P < 0.01), CAP (P = 0.01) and AECB (P = 0.04), significantly elevated levels of serum PCT in comparison to the control group (n = 25), but below the usual cut-off level. Otherwise, no differences (P = 0.5) were observed between PTB (median 0.14 ng/mL) and the control (median 0.11 ng/mL) groups. They suggested that relative to the current cut-off level of 0.5 ng/mL, the serum PCT level is not a useful parameter for the diagnosis of lower respiratory tract infections and PTB. Also, they detected increased median levels of CRP (median 50.5 mg/L) in PTB patients. In the other study, Prat et al. (21) found low PCT values in patients with PTB (0.38 ng/mL, n = 13) and in the control group (0.35 ng/mL, n = 24). They have shown no correlation between PCT level and PTB. Cakir et al. (22) found that relative to the current cut-off level of 0.5 ng/mL, PCT concentration is not a useful parameter for the diagnosis of patients with tuberculous pleurisy (n = 18) because there were PCT levels in patients with tuberculous pleurisy that were below the current cut-off level but were significantly different from those of the nontuberculous pleuritis (n = 10) group. They also detected no statistical correlation between PCT and CRP levels in tuberculous pleuritis and nontuberculous pleuritis groups. In contrast to these studies, a serum mean PCT level of 0.76 ± 0.20 ng/mL was found in 30 patients with active PTB by Kandemir et al. (18). They found a significant difference (P < 0.001) between patients with active PTB and the control group (0.30 ± 0.114 ng/mL).

As reported in the above studies, when the patient population is limited, the predictive values of serum PCT levels in patients with PTB were variable. Our findings are in accordance with the report of Kandemir et al. (18) who found increased PCT levels in patients with active PTB. Likewise, Gendrel et al. (23) and Gendrel and Bohuon (24) determined that when infection is locoregional or single-organ confined without a systemic response of the inflammatory reaction, PCT is slightly or moderately increased. In our study, if we consider the serum PCT cut-off levels of 0.5 ng/mL, then the sensitivity and specificity will be 41.3% and 100%, respectively. We conclude that PCT is a specific but poorly sensitive marker of adult patients with PTB. It has also been recently reported that sensitivity was low (in contrast to a high specificity) with the use of a cut-off level of 0.5 ng/mL; however, improved sensitivity could be obtained after reducing the cut-off level (22).

In the current study, we concluded that the serum PCT level is not a useful indicator in the diagnosis of acute PTB because of its low sensitivity value (41.3%) and in most cases (58.7%) is not capable of overcoming the cut-off level even if statistically meaningful results were obtained. The PCT levels of the patients after 6 months ATCT were found to have decreased to the normal range. Early diagnosis of acute active PTB is very important for public health. However, serum PCT levels lack the necessary sensitivity and cannot be substituted for microbiology, clinical and radiological data. Further studies are necessary to assess the potential value of PCT in comparison with other acute phase proteins, such as amyloid protein A and fibrinogen, for monitoring treatment response and disease activity in cases with PTB. The kinetics of these parameters may help elucidate the availability of PCT.

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