Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

The Impact of Treatment on Serum Level of Procalcitonin in Patients with Active Pulmonary Tuberculosis

Hassan Ghobadi [1], Shahrzad M. Lari[2], Firouz Amani [3], Shahram Habibzadeh[4]*, Amirhosein Karimi [5], Farhad Pourfarzi [6]

[1] *Pulmonologist, Department of Internal Medicine (Pulmonary Division), Ardabil University of Medical Sciences, Ardabil, Iran*
[2] *Pulmonologist, COPD Research Center, Ghaem Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3] *Community Medicine Specialist, Ardabil University of Medical Sciences, Department of Community Medicine, Ardabil, Iran*
[4] *Infectious Disease Specialist, Department of Infectious Disease, Ardabil University of Medical Sciences, Ardabil, Iran*
[5] *General Practitione, Ardabil University of Medical Sciences, Ardabil, Iran*
[6] *Community Medicine Specialist, Department of Community Medicine, Ardabil University of Medical Sciences, Ardabil, Iran*

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 16 Aug 2014
Revised: 21 Jul 2014
Accepted: 29 Sep 2014

Keywords:
Inflammatory Marker
Procalcitonin
Pulmonary Tuberculosis

ABSTRACT

Introduction: About one third of the world's population is infected with tuberculosis (TB) and each year, about 1.5 to 2 million people die from TB. Procalcitonin (PCT) is an inflammatory marker that its level has variable results. There are some discussions in the utilization of PCT as a diagnostic marker in active pulmonary TB. The aim of this study was to compare serum PCT before and after treatment in patients with pulmonary TB.

Materials and Methods: This study was conducted on patients with pulmonary TB. Data were collected using a check list. The serum level of PCT was measured by ELISA test at the beginning and after six months of treatment. All data were analyzed using SPSS 16.

Results: Forty-two patients with active pulmonary TB entered in this study. The mean age of the patients was 45.48±12.54 years and 54.8% of them were male. Most of the patients (59.5 %) were rural inhabitants. There was a family history of TB in 26% of patients. The most common symptom (45.2%) was cough. Mean PCT prior to treatment was 1.25±0.98 ng/ml. and 81% of the patients had PCT higher than 0.5 to 5. After treatment PCT level reduced significantly (P<0.001). The mean erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) before treatment were 45.88±21.87 and 7.16±3.98 respectively that were reduced significantly after treatment (P<0.001). Neutrophil counts before treatment was 6221±3161 Cells per ml. and decreased statistically significant after treatment (P=0.01).

Conclusion: Our results showed that the PCT levels in pulmonary TB were high in active disease and reduced after treatment. PCT level may be used for follow-up as a discriminative marker between active and cured pulmonary TB and predict treatment response, although the PCT assay cannot be substituted for microbiological and pathological data.

►*Please cite this paper as:*
Ghobadi H, Lari SM, Amani F, Habibzadeh Sh , Karimi A H, Pourfarzi P. The Impact of Treatment on Serum Level of Procalcitonin in Patients with Active Pulmonary Tuberculosis. J Cardiothorac Med. 2014; 2(4): 238-242.

Introduction

Tuberculosis (TB) is one of the important causes of mortalities in developing countries and is one of the 8 leading cause of death due to diseases in the world. In 2010, about 8.8 million people worldwide were infected with TB and 1.4 million people will annually die from the disease (1). The World Health Organization estimates that approximately one-third of the world's population are infected with TB (latent TB) or at the disease risk (2).

Most people diagnosed with TB are living in developing countries (3). Despite of medical advances, pulmonary TB is still one of the causes of death and disability in our communities (4).

**Corresponding author:* Shahram Habibzadeh, Infectious Disease Specialist, Department of Infectious Disease, Ardabil University of Medical Sciences, Ardabil, Iran. Tel: +98 9144514670; E-mail: s.habibzadeh@arums.ac.ir

The diagnosis of TB, as the first step in the treatment of patients, has an important and special status. Despite the existence of various diagnostic methods, detection of mycobacterium tuberculosis (in direct smear and staining) is still the only reliable method for diagnosis of tuberculosis in developing countries. Conventional diagnostic methods including sputum smear, culture and pathologic study had some limitations (3, 5). Therefore, the advanced methods for rapid diagnosis of microbe are clear. Biomarkers as diagnostic tests to determine the risk of developing disease, guidance the treatment, and determine the stage of disease progression are being used (6).

Procalcitonin (PCT) is a propeptide calcitonin hormone consists of 116 aminoacids with a molecular weight of 13 KDa , which is secreted from neuroendocrine cells in the thyroid gland and from the liver and lung in response to endotoxins and tumor necrosis factor-α (TNF-α) (7-9). This peptide cannot be detected in the serum of healthy subjects and primarily it increases in the serum of patients in response to infectious disease. The serum level of PCT has a correlation with the severity of pulmonary infections and also prognosis of patients after pulmonary infection (10- 12).

PCT has been used as a biomarker to differentiate viral from bacterial infections, a guide for respiratory infections, for evaluating the response to treatment of bacterial infections in areas where TB incidence is not high (7).

In a study by Kang and colleagues, serum PCT was lower in patients with TB disease compared to pulmonary bacterial infection (7). Rasmussen and colleagues found that PCT levels in TB patients were higher compared with the healthy control group. Although its level was lower in comparison with patients with pneumonia and he concluded that the PCT can be used to predict mortality of TB patients (13). In a study demonstrated by Ugajin and colleagues in patients infected with TB, the serum level of PCT was low and the level higher than 0.5 ng/ml was associated with poor outcome in patients (14).

The purpose of this study was to evaluate the serum level of PCT in patients with active pulmonary TB before treatment and compare with the level after successful anti- tuberculosis treatment for determining the role of PCT an inflammatory marker in active pulmonary TB.

Materials and Methods

In this semi-experimental study, 42 patients with active pulmonary TB, based on positive smear of sputum or bronchoalveolar lavage (BAL) for Mycobacterium tuberculosis were enrolled into this study from September 2011 to September 2012 in Internal Medicine department of Ardabil University of Medical Sciences. For all patients before treatment, a check list included demographic information was collected. Then, serum samples were obtained to check complete blood counts (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum PCT level. At the end of the sixth month of the treatment, serum samples were collected for laboratory examination.

This study was approved by the ethics committee of Ardabil University of Medical Sciences and informed consent was received from all patients.

Procalcitonin test

Samples were prepared according to the standards set. Firstly, labeled monoclonal antibodies were added to the additional samples and waited for reaction for 60 minutes at 37 °C. The samples were washed and chromogen solutions were added to them and were awaited for 10 min at 37°C for reactions. After 10 minutes, the preventive solution was added to the sample. And then, the optical dentist (OD) level of samples were measured under light with a wavelength of 450 nm. The degree of PCT concentration in each sample was calculated based on the standard curve graph. All of these steps were done automatically by a machine (TKA ELISA) made in Italy. In this study, we used Human PCT ELISA Kit made in the U.S.

Statistical Analysis

After doing the experiments and completing the check lists, the data were inserted into SPSS statistical analysis software and then, it was analyzed using statistical methods including Chi-Square and Paired Samples T–test. For evaluating the correlation between variables, Pearson correlation test was used. In all analyses, the P value lower than 0.05 was considered significant.

Results

Out of 42 patients, 55 percent were men and 45 percent were women. The mean age of the patients was 45.48±12.54 and 30 cases, (71/4%), were between 35 to 65 years. Agriculture and farming were the most frequent job among the subjects. Two patients (4/8%) had previous TB disease. Eleven patients (26/2 %) had a positive family history for TB. Cough was the most common complaint among the patients in their [19 cases (45/2%)] (Table 1).

The mean PCT levels before and after the treatment were 1.25±0.98 ng/ml and 0.4±0.11 ng/ml, respectively (P<0.001). The mean ESR in the first hour before treatment was 45.8±21.9 and after treatment was 14.38±10.25 (P<0.001).

Table 1. Patients' demographic parameters

Parameters	Values
Age in years (mean ± SD)	45.48±12.54
Male/Female	23/19 (55%/45%)
Rural/Urban	25/17 (59%/41%)
Married/Unmarried	34/8(80%/20%)
History of Smoking(no.)	9(21%)
History of Familial TB(no.)	11(26%)
Symptom of cough(no.)	19(45%)

Table 3. The correlation between PCT and the research laboratory findings of the subjects

On admission	PCT	
	Correlation	P Value
ESR	– 0.07	0.64
CRP	0.07	0.64
Neutrophil counts(ml)	– 0.26	0.10

Correlation analyses were done by Pearson correlation test

After therapy	PCT	
	Correlation	P Value
ESR	– 0.01	0.57
CRP	– 0.03	0.87
Neutrophil counts(ml)	0.09	0.59
Lymphocyte counts(ml)	– 0.28	0.08

Correlation analyses were done by Pearson correlation test

Analysis of the data showed that the amount of the ESR was significantly reduced with treatment (P<0.001) (Figure1 and 2).

It was also observed that 52.4% of the patients before treatment had t ESR between 30-60, and after treatment 90 percent had their ESR below 30.

The mean CRP was 7.16±3.98 mg/lit before the treatment and it was 3.13±1.34 mg/lit after the treatment. The difference was statistically significant (P<0.001). The results also showed that before treatment in 61.9% of patients, CRP was above 5 while after treatment in 95 percent of patients was below 5. Number of the neutrophils before treatment were6221±3161 cell/ml and after treatment 4411±2756. Also after the treatment the number of neutrophils reduced significantly (P=0.01). Lymphocytes were also counted and the results showed that they were 3528±1623 in number before treatment and 1557±530 after the treatment. After the treatment the number of the lymphocytes reduced and it was statistically significant (P<0.01) (Table 2).

The results suggested that there was no significant correlation between PCT with age and gender (P=0.47 and P=0.96 respectively). There was no significant correlation between ESR and CRP before treatment with PCT level in patients (P=0.23 P=0.74 respectively); there was also no significant correlation between ESR and CRP after treatment with PCT level in patients (P=0.29 P=0.86 respectively). The serum PCT level in 81% of the patients before the treatment was 0.5ng/ml to 5ng/ml. At the end of the study after examining PCT level in patients before and after the treatment and analyzing the results with

Table 2. Comparison of the results in patients before and after the treatment

Parameters	Onadmission	After terapy	P Value
PCT in ng/ml (mean±SD)	1.25±0.98	0.4±0.11	P<0.001
ESR In mm/first hour (mean±SD)	45.8±21.9	14.38±10.25	P<0.001
CRP in mg/L (mean±SD)	7.16±3.98	3.13±1.34	P<0.001
WBC counts/ml (mean±SD)	12402±4445	8185±4594	P<0.001
Lymphocyte counts/ml (mean±SD)	3225±1623	1557±530	P<0.001
Neutrophil counts/ml (mean±SD)	6221±3161	4411±±2756	P=0.01

PCT: procalcitonin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: white blood cell

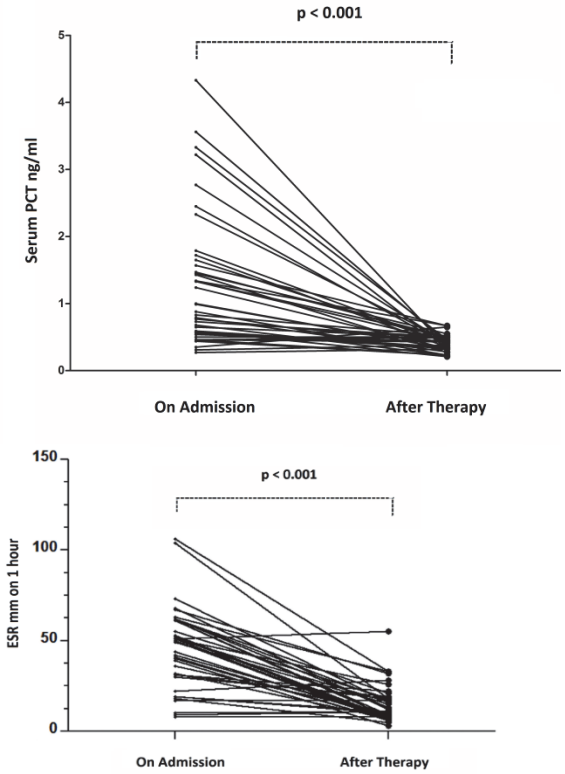

Figure 1 and 2. The mean serum level of ESR and PCT in patients before and after treatment

Paired Sample Test, it was observed that after the treatment the level of PCT was reduced significantly (P<0.001). The relation between PCT and the research laboratory findings of the subjects before and after the treatment all are included in Table 3.

Discussion

The results of this study indicate that serum level of PCT in patients with active pulmonary tuberculosis has increased and this inflammatory marker can be used as a marker to distinguish active pulmonary tuberculosis from convalescent state, especially in countries with high prevalence of tuberculosis and in patients with clinical suspicion of TB. PCT can be used as a serum

inflammatory marker.

Although the high serum level of PCT is not a definite clue for diagnosing tuberculosis, it can be interpreted in favor of tuberculosis. Additionally, this inflammatory marker can be used in assessing the response to treatment. Before treatment, 81 percent of patients had a PCT higher than 0.5 (cut of point in present study) which was reduced after treatment. Similar results have been found in some other studies (11-14).

Although it is known as a marker of bacterial infection, the use of PCT in the diagnosis of infections is still controversial (15). Most studies on the use of PCT have been focused on distinguishing inflammation caused by the infection from non-infectious inflammatory factors (16). PCT level rises in bacterial infections (13) and low PCT indicates low risk of disease mortality (17). The maximum normal PCT level of serum is 0.5 ng/ml and for higher amounts the initiation of therapy is recommended (18).

The production of PCT in patients with tuberculosis is not still known (10). Cellular defense mechanism in TB patients depends mainly on CD4+ T lymphocytes; these cells are multiplied and they produce numerous cytokines containing TNFα. Lipoarabinomanan is another molecule in the mycobacterium cell wall which is involved in the pathogen-host interaction and facilitates the survival of mycobacterium tuberculosis in macrophages (5, 19). In patients with TB, interleukin-1 (IL-1), IL-6, IL-10, TNFα, and other inflammatory cytokines increase and these cytokines can increase PCT independent from bacterial endotoxin and therefore they can explain the increase of PTC in cases other than bacterial infection (10, 20). Interferon γ (INF γ) is an important cytokine for inhibition of the mycobacterium and it can cause the production of PCT in patients with tuberculosis (14).

In Baylan's study, PCT level has specifically increased in patients with tuberculosis. This study showed that PCT level is a specific but low-sensitive marker in patients with pulmonary tuberculosis (10). In Schleicher et al. study 59% of patients with TB had high PCT; they have concluded that this marker has been helpful in patients with tuberculosis (20).

Some have indicated that PCT in serum or pleural fluid may not be a useful parameter in the diagnosis of TB pleurisy. Although in patients with TB pleurisy the PCT level has increased more than non TB pleurisy, further studies are recommended (15). Malek Mohammad has shown that PCT is not a useful parameter for the diagnosis of TB pleurisy (12). In his study PCT amounts of pleural fluid have been investigated while in present study the serum level of PCT is examined.

In this study the mean age was 45.48±12.54 and the majority of cases (71%) were aged between 35 to 65 years. Age and sex patterns in present study are different from other studies (7, 10,21) and the mean age was low (10,13). However there have been studies consistent with this study in which most patients were men (13) and the mean age was high (11,21).

Since the majority of patients (59.5%) were from rural areas, the fact is that the population density in rural homes is higher and therefore the close contacts of family members are higher compared with urban population.

The findings of the study show that 11 patients had a family history of TB among their close relatives who have been diagnosed with active TB and this puts more emphasis on latent TB infection treatment or medications and must be considered in clinical guidelines for treatment of TB patients.

In this study the mean ESR and CRP decreased significantly with treatment ($P<0.001$). The neutrophil count ($P=0.01$) and lymphocytes count ($P<0.001$) also decreased by treatment and this is in concordant with the results of other studies (7, 13). It can be concluded that although ESR and CPR are not diagnostic for TB, they are important clues in patients with TB and in patients with high ESR, CRP, and pulmonary symptoms, TB must be considered in differential diagnosis and additional diagnostic tests for sputum smear and sputum culture must be taken.

The limitations of this study are the low sample size (because of lesser prevalence of pulmonary tuberculosis) and the lack of control group which can reduce the validity of study. A further study with a larger sample size and with control group is suggested.

Conclusion

This study shows that PCT level in patients with active pulmonary TB in the city of Ardabil has decreased after treatment. So it can be used for follow-up as a discriminative marker between active and cured pulmonary TB and predict treatment response and observing their recovery process although it cannot be an alternative for bacteriological and pathological diagnosis.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Lange C, Sester M. TB or not TB: the role of immunediagnosis. Eur J Immunol. 2012; 42: 2840-3.
2. Young DB, Gideon HP, Wilkinson RJ. Eliminating latent tuberculosis. Trends Microbiol. 2009; 17:183-8.
3. Delogu G, Zumbo A, Fadda G. Microbiological and immunological diagnosis of tuberculous

spondylodiscitis. Eur Rev Med Pharmacol Sci. 2012; 16:73-8.
4. Baganha MF, Pego A, Lima MA, Gaspar EV, Cordeiro AR. Serum and pleural adenosine deaminase. Correlation with lymphocytic populations. Chest. 1990; 97:605-10.
5. Trajman A, Pai M, Dheda K, van Zyl Smit R, Zwerling A, Joshi R, et al. Novel tests for diagnosing tuberculous pleural effusion: what works and what does not? Eur Respir J. 2008; 31:1098-106.
6. Maertzdorf J, Weiner J 3rd, Kaufmann SH. Enabling biomarkers for tuberculosis control. Int J Tuberc Lung Dis. 2012; 16:1140-8.
7. Kang YA, Kwon S-Y, Yoon HI, Lee JH, Lee C-T. Role of C-Reactive Protein and Procalcitonin in Differentiation of Tuberculosis from Bacterial Community Acquired Pneumonia. Korean J Intern Med. 2009; 24:337-42.
8. San Jose ME, Valdes L, Vizcaino LH, Mora T, Pose A, Soneira E, et al. Procalcitonin, C-reactive protein, and cell counts in the diagnosis of parapneumonic pleural effusions. J Investig Med. 2010; 58:971-6.
9. Wang CY, Hsiao YC, Jerng JS, Ho CC, Lai CC, Yu CJ, et al. Diagnostic value of procalcitonin in pleural effusions. Eur J Clin Microbiol Infect Dis. 2011; 30: 313-8.
10. Baylan O, Balkan A, Inal A, Kisa O, Albay A, Doganci L, et al. The predictive value of serum procalcitonin levels in adult patients with active pulmonary tuberculosis. Jpn J Infect Dis. 2006; 59:164-7.
11. Naderi M, Hashemi M, Kouhpayeh H, Ahmadi R. The status of serum procalcitonin in pulmonary tuberculosis and nontuberculosis pulmonary disease. J Pak Med Assoc. 2009; 59:647-8.
12. Malekmohammad M, Naghan PA, Tabarsi P, Pourabdollah M, Mohajerani SA, Fotoohi F, et al. The diagnostic value of pleural effusion pro-calcitonin level in different etiologies of exudative pleural effusion. Afr J Microbiol Res. 2012; 6:3237-41.
13. Rasmussen T, Sogaard O, Camara C, Andersen PL, Wejse C. Serum procalcitonin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2011; 15:251-6.
14. Ugajin M, Miwa S, Shirai M, Ohba H, Eifuku T, Nakamura H, et al. Usefulness of serum procalcitonin levels in pulmonary tuberculosis. Eur Respir J. 2010; 37:371-5.
15. Cakir E, Deniz O, Ozcan O, Tozkoparan E, Yaman H, Akgul EO, et al. Pleural fluid and serum procalcitonin as diagnostic tools in tuberculous pleurisy. Clin Biochem. 2005; 38:234-8.
16. Nyamande K, Lalloo U. Serum procalcitonin distinguishes CAP due to bacteria, Mycobacterium tuberculosis and PJP. Int J Tuberc Lung Dis. 2006; 10:510-5.
17. Kosanke R, Beier W, Lipecky R, Meisner M. Clinical Benefits of Procalcitonin. Tanaffos. 2008; 7:14-8.
18. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, et al. Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia: A Randomized Trial. Am J Respir Crit Care Med. 2006; 174:84-93.
19. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol. 2002; 168: 4620-7.
20. Schleicher G, Herbert V, Brink A, Martin S, Maraj R, Galpin J, et al. Procalcitonin and C-reactive protein levels in HIV-positive subjects with tuberculosis and pneumonia. Eur Respir J. 2005; 25:688-92.
21. Hashemi A, Shojaei H, Heidarieh P, Aslani MM, Naser AD. Genetic diversity of Iranian clinical isolates of Mycobacterium tuberculosis. New Microbiol. 2012; 35:61-5.