Procalcitonin levels in Sjögren syndrome

Bahar Arican Tarim[1], Mehmet Engin Tezcan[2], Asuman Orcun[3], Mehmet Aliustaoglu[1], Ozcan Keskin[1].
[1]Department of Internal Medicine, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[2]Department of Rheumatology, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[3]Department of Biochesmistry, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Background: procalcitonin (PCT) is a polypeptide secreted as a response a bacterial stimulus. PCT serum concentrations are increased also in some autoimmune diseases. At the best of our knowledge, there is no study in literature that evaluated PCT values in patients with primary Sjögren's syndrome (pSS). The aim of this paper is to measure PCT values in pSS and to determine if these are related to the disease activity.
Methods: this is a case-control study. Two groups of subjects were included: 48 patients with pSS, who met American College of Rheumatology 2012 Classification Criteria for Sjögren's syndrome and 53 healthy subjects as control group (without any acute or chronic disease). The subjects with possible infectious disease were excluded on the basis of their clinical evaluation and laboratory data. Serum PCT values were measured by electrochemiluminometric method. PCT values have been compared between the groups; the correlation between disease activity, measured by Sjögren's syndrome disease activity index (SSDAI) and PCT levels was evaluated.
Results: PCT values in pSS group were within the reference range, but significantly higher than those measured in the control group [median (interquartile range) values were 0.036 ng/mL (0.031-0.044) and 0.020 ng/mL (0.020-0.020) respectively], ($p<0.001$). No correlation was found between disease activity and PCT values ($p=0.63$).
Conclusions: on the basis of the presented results, PCT could be a candidate marker for differentiating disease activity from the presence of an infection in pSS patients. Future studies in pSS patients with infectious diseases could possibly demonstrate the role of PCT in this context.

INTRODUZIONE

Procalcitonin (PCT) is a polypeptide secreted as a response to a bacterial stimulus. It is considered and used in clinical practice as an early and sensitive marker of infection (1). It was shown that endotoxins, cytokines and bacterial lipopolysaccharides are strong stimulators of PCT excretion. In healthy subjects, PCT is usually <0.1 ng/mL and in case of infection a rise over 0.5 ng/mL could be observed (1).

PCT values might also increase in inflammatory diseases without concomitant infection; however, in inflammatory diseases the PCT plasma concentration usually does not reach the values measured in infections (2-6).

In the rheumatology field, a number of studies have investigated the PCT levels in autoimmune diseases (2-20). The results suggest that in some autoimmune diseases, a certain amount of increase in PCT levels can be observed despite a lack of concomitant infections. The differential diagnosis between infection and disease activation is important in autoimmune diseases. Several studies have evaluated the role of PCT in excluding infection from disease activity (7, 10, 18-20). At the best of our knowledge, there is no study in the English literature concerning PCT values in patients with primary Sjögren's syndrome (pSS) and evaluating whether PCT values can be used to differentiate disease activation from infection in these patients.

The aim of this study is to compare PCT values in pSS patients with a group of healthy controls and to evaluate the possible correlation levels and disease activity.

Corrispondenza a: Mehmet Engin Tezcan, MD., Kartal Dr. Lutfi Kirdar Training and Research Hospital, Department of Rheumatology, Kartal, 34680, Istanbul-TURKEY, Tel. +902164583000, E-mail: engintez@yahoo.com

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METHODS

48 patients with pSS were enrolled in the study. Patients were admitted to Dr. Lutfi Kirdar Kartal Training and Research Hospital, Istanbul (Turkey) rheumatology outpatient clinic in one year period from June 2016 to June 2017. All patients met the 2012 criteria of the American College of Rheumatology for classification of Sjögren's Syndrome (21). 53 healthy subjects, without any acute or chronic diseases were appointed as control group. All the subjects were referred to the Internal Medicine outpatient clinic of the same hospital for a routine check-up. Patients and controls were matched for age, sex and educational level.

Patients and controls were evaluated for the presence of infection on the basis of their medical history and physical examination. Subjects with active infection or those with clinical suspicion of infection were excluded. Patients with other autoimmune disease or chronic inflammatory diseases, or who had a history of surgery or hospitalization in the last few months, or were using antibiotics at the time of the study were also excluded.

The patients underwent complete physical examination and laboratory tests including complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein, urine analyses and PCT. PCT concentrations were assessed in serum samples and measured by Roche Modular E-170 device by an electrochemiluminometric immunoassay within 24 hours from the blood collection. During the first incubation a biotinylated monoclonal PCT specific antibody and a monoclonal PCT specific antibody labeled with a ruthenium complex react with PCT to form a sandwich complex. After addition of streptavidin-coated microparticles, the complex binds to the solid phase via interaction of biotin and streptavidin. Microparticles are then magnetically captured onto the surface of the electrode and unbound substances are removed with a wash solution. Application of a voltage to the electrode induces chemiluminescent emission that is measured by a photomultiplier. PCT concentrations are finally determined via a calibration curve. The analytical sensitivity of the method is ≤0.02 ng/mL; the functional sensitivity is 0.06 ng/mL.

Disease activity was calculated by Sjögren's Syndrome disease activity index (SSDAI) (22). The two groups were matched according to their educational level for ensuring the reliability of the patient-based items in SSDAI.

The study obtained the approval from the local ethic committee and it has been carried out as per the Helsinki declaration as revised in 1996. All the participants gave informed consent before they were included in the study.

Statistical analyses

Statistical analyses were carried out by SPSS (17.0, Chicago, IL, USA) program. Distribution of numerical variables was evaluated by Kolmogorov-Smirnov test. All categorial variables were non-normally distributed. Numerical variables were compared with Mann-Whitney U test; Chi-square test was used to compare categorical variables. Numerical variables were summarized by median (interquartile range) values. The presence of correlation between PCT and disease activity was determined by Spearman's correlation coefficient. A value of $p < 0.05$ was considered significant.

RESULTS

A total of 101 participants were included in this study; 48 of them were patients with pSS. PCT level was found statistically higher in pSS group ($p<0.001$). However, none of the pSS patients had PCT value higher than 0.1 ng/mL; unlike, one subject in the control group had PCT value higher than 0.1 ng/mL. Furthermore, patients with pSS had higher creatinine levels and lower platelets levels as compared to the controls ($p=0.02$). However, creatinine and platelets of all subjects were within the reference range. All other demographic and laboratory parameters did not differ between the two groups (Table 1). None of the patients had extra glandular involvement at the time of the study. Moreover, all patients were on hydroxychloroquine and none were on steroids at the time of the study.

Furthermore, no correlation was detected between disease activity and PCT levels ($p=0.63$).

DISCUSSION

In this study, the levels of PCT in pSS patients were compared with those measured in healthy subjects and the correlation of PCT blood concentration with disease activity was investigated. PCT levels were found higher in pSS patients; however, patient's PCT values were within the reference range and not correlated with disease activity.

In patient with autoimmune diseases, the differential diagnosis between infection and increased disease activity is generally difficult. Several studies investigating the contribution of PCT in differentiating disease activity from the infection are available (7, 10, 18-20).

Sato et al, report that PCT values in rheumatoid arthritis patients do not increase during acute exacerbation period. However, PCT levels increase significantly in these patients during bacterial infections (14).

Furthermore, it was shown that there was no correlation between the PCT levels and systemic lupus erythematosus disease activity. It was thus suggested that PCT values could be used to differentiate infection from disease activity in febrile patients (16).

In another study carried out in familial Mediterranean fever patients, PCT values increased non-significantly during attack period (20). Also in Behçet's disease, PCT blood concentrations did not differ between patients and healthy controls (7). It was also observed that PCT

Table 1
Demographic characteristics and laboratory results of the subjects.

	Sjögren's disease patients (n=48)	Healthy control subjects (n=53)	p-value
Gender (M/F)	3/45	2/51	0.66
Age, years	53.50 (48.50 - 58.75)	50.00 (43.50 - 55.00)	0.04
SSDAI score	1.0 (1.00 - 2.00)	N/A	
Distribution of SSDAI, n (%)			
0	10 (20.8)		
1	18 (37.5)		
2	8 (16.6)		
3	5 (10.4)		
4	2 (4.1)		
4	2 (4.1)		
>5	3 (6.2)		
Domains of SSDAI, n (%)			
Fever	0 (0.0)		
Fatigue	32 (66.6)		
Change in fatigue	11 (26.5)		
Articular symptoms	36 (75.0)		
Cytopenia	0 (0.0)		
Lymphadenopathy/splenomegaly	4 (8.3)		
Vasculitis	0 (0.0)		
Renal involvement	0 (0.0)		
Peripheral neuropathy	0 (0.0)		
PCT, ng/mL	0.036 (0.031 - 0.044)	0.020 (0.020 - 0.020)	**<0.001**
ESR, mm/h	22.0 (12.0 - 31.7)	18.0 (11.0 - 27.0)	0.13
CRP, mg/L	3.2 (3.2-3.2)	3.2 (3.1-3.2)	0.16
Hemoglobin, g/dL	12.5 (11.6 - 13.5)	12.8 (11.9 - 13.5)	0.82
Platelets (10^3/uL)	231 (189 - 278)	265 (226 - 304)	**0.02**
Leucocytes (10^3/uL)	6000 (5400 - 7200)	6700 (5450 - 8000)	0.15
Creatinine, mg/dL	0.66 (0.59 - 0.76)	0.57 (0.52 - 0.62)	**<0.001**
ALT, U/L	18.5 (13.2 - 25.0)	18.0 (13.5 - 25.0)	0.74
AST, U/L	22.5 (19.0 - 25.0)	21.0 (17.5 - 25.5)	0.30

SSDAI, Sjögren's syndrome disease activity index; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; CRP; C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.
Statistically significant P values were shown in bold.
Continues variables were shown as median (interquartiles range).

values increased in active granulomatosis with polyangitis and Still's disease, without presence of infection (4-6).

Tumor necrosis factor-alfa (TNF-alfa), interleukin-1 (IL-1) and interferons are main inducers of PCT secretion. TNF-alfa and IL-1 are not particularly increased in pSS, at odds with what is observed in infectious diseases; TNF is only moderately increased even in the active disease (22). These observations can explain why PCT values are within the reference range (<0.1 ng/mL) in our pSS patients and only slightly higher than the values observed in the control group.

Even if platelet count is lower and creatinine concentrations are significantly higher in pSS patients than in control group, these parameters are within the reference range in both groups. The reasons for these differences could be attributable to drug side effects or disease related autoimmune phenomena.

Our study was mainly designated to evaluate whether the disease activity correlates with PCT values. We did not find any correlation between SSDAI score and the PCT levels. Also, considering that none of the pSS patient show extraglandular involvement, we can conclude that PCT concentrations do not increase with disease activity in our pSS patients. This is probably due to the difference of cytokine expression between bacterial infections and pSS, especially during active disease state. Future studies that evaluate PCT levels in pSS patients with infection could demonstrate the effectiveness of PCT as a reliable marker for screening infection diseases and follow up the treatment response to bacterial infection in pSS.

Functional analytical sensitivity of the kit we used was 0.06 ng/mL. Both patients and controls' median and third quartile PCT values were lower than 0.06 ng/mL. Therefore, the clinical significance of the difference in PCT values between the groups, is unclear even it was statistically significant.

Limitations of this study are the small sample size and lack of Sjögren's disease patient with extra-glandular manifestations.

Future studies including pSS patients with extra-glandular involvement and pSS patients with infectious diseases could give more information about the role of PCT in differentiating disease activity from infection in this patient group.

CONFLICT OF INTEREST:

None.

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