Türk Biyokimya Dergisi [Turkish Journal of Biochemistry–Turk J Biochem] 2014; 39 (1) ; 37–42
doi: 10.5505/tjb.2014.72602

Research Article [Araştırma Makalesi]

Yayın tarihi 30 Mart, 2014 © TurkJBiochem.com
[Published online 30 March, 2014]

Comparison between serum neopterin, procalcitonin, high-sensitivity C-reactive protein concentrations and erythrocyte sedimentation rates of patients with brucellosis and extracellular bacterial infections

[Brusellozis ve ekstrasellüler bakteriyel enfeksiyonu olan hastalarda serum neopterin, prokalsitonin, yüksek duyarlıklı C-reaktif protein konsantrasyonlarının ve eritrosit sedimentasyon hızlarının karşılaştırılması]

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Registered: 22 April 2013; Accepted: 13 November 2013
[Kayıt Tarihi: 22 Nisan 2013; Kabul Tarihi: 13 Kasım 2013]

ABSTRACT

Objectives: The aim of this study was to evaluate neopterin (NPT), procalcitonin (PCT), erythrocyte sedimentation rates (ESR) and high-sensitivity C-reactive protein (hs-CRP) levels in brucellosis and to compare them with extracellular bacterial infections.

Methods: In the study, a total of 89 patients, 50 patients (study group) with acute brucellosis and 39 patients with extracellular bacterial infections (EI group), were included. In EI group, 21 patients had upper urinary tract infection (UTI) while 18 patients had skin and soft tissue infection (SSTI). As well as the appropriate clinic, the patients with positive blood cultures for Brucella spp. or Standard Tube Agglutination test ≥1/160 were diagnosed with brucellosis. Brucellosis and EI groups were compared in terms of ESR, NPT, PCT and hs-CRP.

Results: In study group mean age was 40.64±1.86 (18-66) and in EI group mean age was 51.61±2.68 (18-82). After comparison analysis; ESR (16.5±1.75 vs 40.17±4.52 mm/h, p=0.0001) and hs-CRP (40±8 vs 280±30 mg/L, p=00001) were found lower in the study group than EI group while there was no difference between groups in terms of PCT (p=0.887) and NPT (p=0.688). Additionally, PCT values were higher in patients with UTI than SSTI.

Conclusion: It was seen that NPT and PCT values in brucellosis were not different from extracellular bacterial infections, whereas higher ESR and hs-CRP values could be seen in patients with extracellular bacterial infections. Also, higher PCT values could be seen in patients with urinary tract infections compared to patients with skin and soft tissue infections.

Key words: Brucellosis, neopterin, procalcitonin, High-sensitivity C-reactive protein

Conflict of Interest: We declare that there is no conflict of interest.

ÖZET

Amaç: Bu çalışmanın amacı bruselloz da neopterin (NPT), prokalsitonin (PCT), eritrosit sedimenatasyon hızı (ESR) ve yüksek duyarlılıklı C-reaktif protein (hs-CRP) düzeylerini değerlendirmek ve bunları ekstrasellüler bakteriyel enfeksiyonlarla (EI) karşılaştırmaktır.

Yöntem: Çalışmamıza akut brusellozu olan 50 hasta (çalışma grubu) ve ekstrasellüler bakteriyel enfeksiyonu olan 39 hasta (EI grup), toplamda 89 hasta dahil edildi. EI gruptaki 21 hastada üriner sistem enfeksiyonu (UTI), 18 hastada ise deri ve yumuşak doku enfeksiyonu vardı (SSTI). Uygun kliniğin yanında brusella yönünden pozitif kan kültürü olan veya Standart Tüp Aglütinasyon testi ≥1/160 olan hastalara bruselloz tanısı konuldu. Bruselloz ve EI grupları ESR, NPT, PCT ve hs-CRP açısından karşılaştırıldı.

Bulgular: Çalışma grubunda ortalama yaş 40.64±1.86 (18-66) iken EI grubunda 51.61±2.68 (18-82) idi. Karşılaştırma analizi sonrası PCT ve NPT açısından çalışma ve EI grupları arasında fark bulunamazken, ESR (16.5±1.75 yerine 40.17±4.52 mm/h, p=0.0001) ve hs-CRP (40±8 yerine 280±30 mg/L, p=0.0001) şeklinde çalışma grubunda EI grubuna göre daha düşük olduğu bulunmuştur. Ek olarak PCT değerleri UTI olan hastalarda SSTI olanlara göre daha yüksekti.

Sonuç: Brusellozdaki NPT ve PCT değerlerinin ekstrasellüler bakteriyel infeksiyonlardan farklı olmadığı görülmüş buna karşın ekstrasellüler bakteriyel infeksiyonu olan hastalarda daha yüksek ESR ve hs-CRP değerleri görülebilmektedir. Ayrıca SSTI olan hastalarla karşılaştırdığımızda UTI olan hastalarda daha yüksek PCT değerleri görülebilmektedir.

Anahtar Kelimeler: Bruselloz, neopterin, prokalsitonin, hs- CRP

Çıkar Çatışması: Bu makalede yazarlar arasında çıkar çatışması bulunmamaktadır.

Introduction

Brucellosis is an important infectious disease that can affect many organs and systems. It can be seen at every age and every region worldwide particularly in the Mediterranean region [1]. Turkey is an endemic region for Brucella infections. The mortality of brucellosis is low; however, morbidity rates are much higher [2]. *Brucella spp.* are gram negative intracellular bacteria that firstly invades monocytic cells and cause infection. Transmission is particularly caused by oral ingestion of infected foods, contact with infected animals and aerosol inhalation [3]. Clinically, brucellosis is characterized with non-specific symptoms such as fever, night sweats, loss of appetite, loss of weight, weakness, severe headache and polyarthralgia. Physical findings are based on the duration of disease and can include hepatosplenomegaly, lymphadenopathy, spondilitis and arthritis [4,5]. Because of the different clinical features, in the differential diagnosis, diseases such as miliary tuberculosis, malaria, typhoid fever, adult Still' disease, romatoid arthritis, sacroileitis and lymphoma must be taken into consideration [6].

In the diagnosis of brucellosis methods such as Rose Bengal (RB) test, Standard tube agglutination test (STA) and isolation of bacteria from the blood and tissue samples are the most used methods [7]. On the other hand, to make a diagnosis especially in the chronic illness settings, is not easy and laboratory findings cannot be beneficial at every time [8].

Erythrocyte sedimentation rate (ESR) is a time-honored, although not sensitive and specific, blood test which assesses the degree of erythrocyte aggregation mediated by acute phase proteins, such as fibrinogen and immunoglobulins. It is frequently used and cheap test (9)

Neopterin (NPT) is synthesized by macrophages and dendritic cells that are stimulated by interferon gamma that is secreted by activated T lymphocytes. NPT is considered as an important indicator of cellular immunity. Serum NPT concentration increases in case of acute viral infections, intracellular and extracellular bacterial infections and parasitic infections [10, 11].

Procalcitonin (PCT) is a protein that is consisting from 116 amino acids and a prohormone of calcitonin which is secreted by thyroid gland [12]. PCT is produced as a response to the endotoxins and mediators (i.e. IL1-β, TNF-α, IL-6) that are secreted during the bacterial infections and its secretion increases in correlation with the severity of the bacterial infection [13].

C-reactive protein (CRP) is an acute phase reactant secreted by the hepatocytes and a sensitive indicator of inflammation and tissue injury [14]. High sensitivity CRP (hs-CRP) is not a different test, it is just a method used to measure the very low concentrations of CRP [15]. Significantly increased CRP level is related with infection (most often bacterial) [16].

In this study, we aimed to evaluate the specifity of NPT, PCT, ESR and hs-CRP tests for acute brucellosis by comparing levels of these markers in patients with brucellosis with patients who had extracellular bacterial infections [skin - soft tissue (SSTI) and upper urinary tract infections (UTI)].

Methods

In the study, 50 (study group) with acute brucellosis (symptoms, and clinical presentation time: 0–2 months) (31 male, 19 female) and 39 with extracellular bacterial infections (EI group) (15 male, 24 female), total of 89 patients who admitted to Gaziosmanpasa University, Department of Infectious Diseases Clinic were included. Blood samples were collected by vene puncture, and serum samples were stored at -80 ^{0}C until analysis.

As well as the appropriate clinic, the patients with positive blood cultures for Brucella spp., or patients with specific antibodies at significant titers and/or at least four-fold rise in antibody titer in serum specimens taken over 2 or 3 weeks, were diagnosed as brucellosis. Significant titers were those determined to be ≥1/160 in the standard tube agglutination test (STA) [17].

Brucella abortus M101 (Cromatest, Linear Chemicals, Spain) or *B. melitensis* S99 antigens (Pendik Veterinary Control and Research Institution, Istanbul, Turkey) were used for the standard tube agglutination test.

Sacroileitis was diagnosed with MRI. Patients with pyuria, leukocytosis and high CRP values as well as symptoms associated with upper urinary tract infection (fever, dysuria, tenderness in costovertebral angle etc) were diagnosed as upper UTI. Also, patients with skin lesions associated with at least 2 of inflammatory findings (redness, pain, swelling, warmth) or with purulent exudate as well as fever and elevated CRP values, considered as SSTI.

Diagnostic values of NPT, PCT, and ESR and hs-CRP test methods for brucellosis were evaluated by comparing them with those of patients in the EI group.

Patients were also compared in terms of neutrophil count, hemoglobin (Hb), platelet count (PLT), alanine aminotransferase (ALT) and aspartate aminotransferase activity. At last patients with two different acute bacterial infections (UTI vs SSTI) were compared.

In serum samples of patients, hs-CRP (DIAseurce, Belgium), neopterin (TML, Turkey) and procalcitonin (Eastbiopharm, China) tests were measured using the ELISA kits in accordance with the instructions of the manufacturers. All serum samples were assayed in duplicate. Serum samples of patients were diluted 1:20 before hs-CRP assaying, and further dilution was made for samples with high CRP and finally all results were multiplied by the dilution factor.

The study protocol was approved by the institutional review board of the Gaziosmanpasa University, Tokat, Turkey (IRB No:11-BADK-044, 2011).

Statistical Analysis

In our study, continuous data were expressed as mean ±standard deviation or median, interquartile range according to parametric or non-parametric test. For the discrete (qualitative) data frequency and percentage distributions are given. In our study, for the comparison of differences between the averages of the variables that are mentioned with measurement and that have dimension number (k=2) t-test for independent samples was used. In situation when the data doesn't comply with normal distribution (when p <0.05 according to the Levene's test) "Mann Whitney U test" which is a non-parametric test was used. In our study p≤0,05 is considered as significant.

Results

Of the 50 patients with brucellosis, 31 (62%) were male, 19 (38%) were female. Of the 39 patients in EI group 15 (38.5%) were male and 24 (61.5%) were female. Average age of the brucellosis and EI groups were found to be 40.64±1.86 and 51.31±2.68 respectively (Table 1).

Firstly, neutrophil counts were compared and mean neutrophil count in the EI group (10070±602/mm^3) was found to be higher than that of brucellosis group (7444±277/mm^3) (p=0.0001). And in the brucellosis group hemoglobin values were found to be higher than EI group (p=0.0001). Any difference between the brucellosis and EI groups was not detected in scope of PLT, AST, ALT.

When the brucellosis and EI groups were compared in terms of ESR, PCT, NPT and hs-CRP; ESR and hs-CRP were found to be significantly higher in EI group (for ESR: p=0,0001; for hs-CRP: p=0,0001). Six out of 50 patients (12%) with brucellosis had PCT levels above the threshold of 0,1 ng/mL while 6 out of 39 (15.4%) patients in EI group had PCT levels above the threshold. Any differences between two groups were not detected in terms of PCT (p=0.887) and NPT (p=0.688) (Table 1).

A ROC analysis was performed to determine the most appropriate hs-CRP concentration and ESR value to define brucellosis patients. Areas under ROC curve (AUROC) for hs-CRP and ESR were 0.836 (95% CI:0,742-0,906) and 0,82 (95% CI:0,725-0,894), respectively. For diagnosing brucellosis, hs-CRP concentrations equals to 87 mg/L or below this threshold and ESR equals to 22 mm/h or below this value, revealed sensitivities of 92%, 80% and specificities of 74,36%, 76,92%, respectively (Figure 1).

EI group consisted of 21 patients with UTI and 18 patients with skin and soft tissue infections. It was observed that PCT levels were higher in the UTI group when compared with the SSTI group (p=0.049). There were no differences between 2 groups in terms of other inflammatory parameters.

Table 1. Comparison of brucellosis and EI groups (EI: Extracellular bacterial infection)

Variables	Brucellosis group (n:50)	EI group (n:39)	p
Female n(%)	19 (38)	24 (61.5)	**0.028**
Age	40.64±13.19	51.31±16.78	**0.001**
ESR (mm/h)	13.5[8-21]	30[23-50]	**<0.001***
PCT (ng/mL)	0.20±0.53	0.18±0.41	0.887
NPT (nmol/L)	37.70±32.62	40.49±32.11	0.688
Hs-CRP (mg/L)	21[7-54]	312[76-478]	**<0.001***
Neutrophil (/mm^3)	7400[5800-8900]	9600[7900-13200]	**<0.001***
Hb (g/dL)	13.72±1.81	12.17±1.61	**<0.001**
PLT (x10^9/L)	233.34±68.54	263.30±96.79	0.091
AST (U/L)	31.46±31.27	24.74±14.08	0.216
ALT (U/L)	31.20±30.28	23.28±12.83	0.130

Data were presented as n (%), mean±standard deviation and median [IQR].
*: Mann Whitney U test was performed.

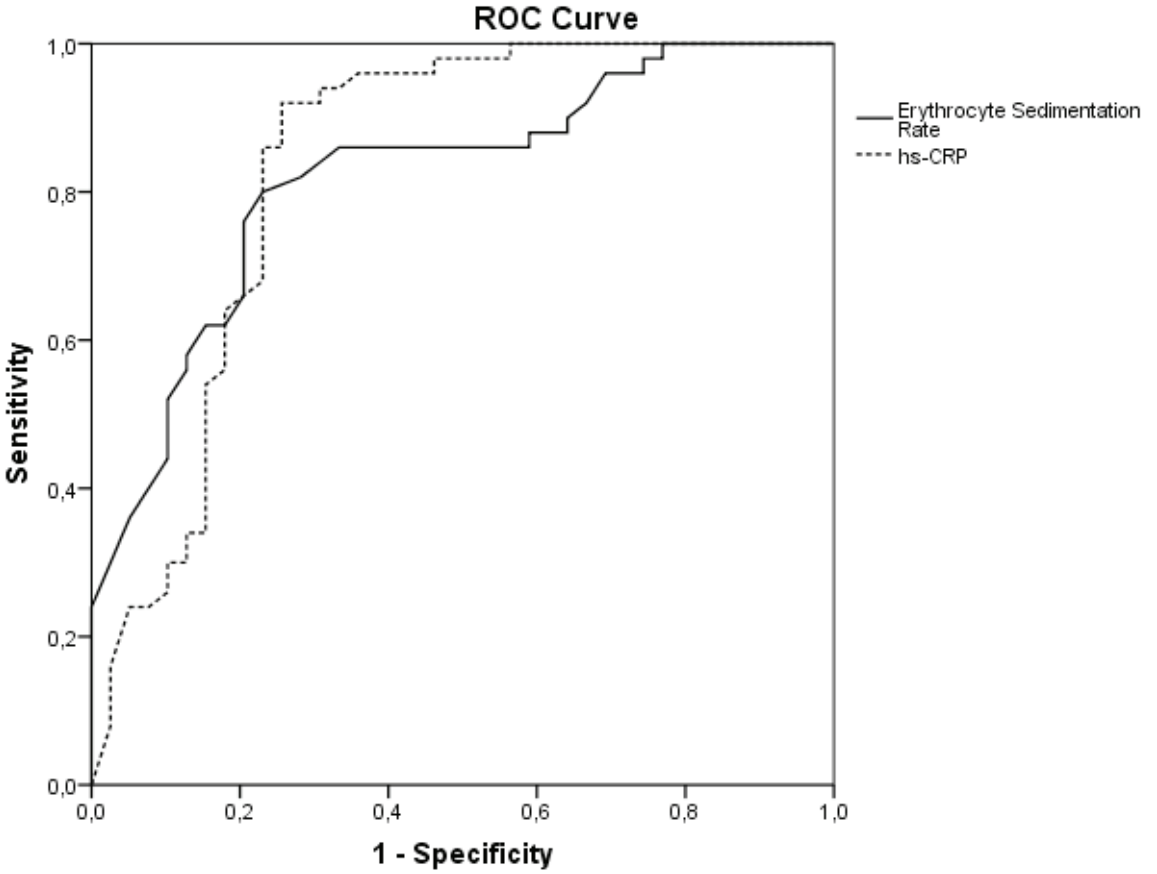

Figure 1: ROC curves of hs-CRP and ESR for diagnosing brucellosis (Areas under ROC curves (AUROC) for hs-CRP and ESR were 0.836 (95% CI:0,742-0,906) and 0,82 (95% CI:0,725-0,894), respectively.)

Discussion

As a laboratory finding, leucopenia, thrombocytopenia, anemia and rarely leukocytosis (particularly at those with focal complications) can be seen in patients with brucellosis. Slight - moderate increase in ESR and CRP and moderate increase in liver enzymes can be seen [18].

In our study, neutrophil counts of 96% of the patients with brucellosis were found to be normal (4000-10000 /mm^3), anemia was found in one patient (Hb ≤11 g/dl). As predicted neutrophil count was significantly higher in EI group when compared with the brucellosis group (p=0.0001). In scope of Hb values, they were found to be significantly higher in the brucellosis group. This was considered to be related with the younger patient context of the study group. In our region risk for exposure to brucella due to occupational risks (farmers, veterinarians, butchers etc.) is high in young – middle age groups.

AST (31,46±4,42 U/L) and ALT (31,20±4,28 U/L) values of our brucellosis patients were in normal limits. Between brucellosis and EI groups any differences were not detected in terms of PLT, AST and ALT. In a retrospective study conducted in our country in which 1028 cases of acute brucellosis were included, anemia was observed at 43% of the patients and leukocytosis at 9,5%, thrombocytopenia at (11,8%) and transaminase increase at 31,3% of patients [19].

Eini *et al.* reported that leukocytosis and anemia was observed at 20,8% and 14,7% of the patients with brucellosis, respectively [20]. On the other hand at the study of Roushan *et al.* leukocyte values were found to be normal at the 84,5% of the patients, same as at the study of Haddadi *et al.* leukocyte values were shown to be normal in most of the patients [21, 22].

In our study, value of NPT in the diagnosis of brucellosis and in the differentiation of brucellosis from the other bacterial infections was evaluated. Neopterin level was significantly elevated in the patients with brucellosis (37,70±4,61 nmol/L). In similar studies in our country, NPT levels were found to be higher in patients with brucellosis when compared with the healthy control subjects and it has been suggested that monitoring NPT can be beneficial in monitoring the treatment response [2,8,14].

As a difference in this study, we included patients with extracellular bacterial infection as control subjects. In our study, NPT levels were also high in the control group (40,49±5,14nmol/ml) but there was not any statistically significant differences between the 2 groups (p=0,688). For this reason we suggest that NPT test can be used

in the diagnosis of acute brucellosis but will not be beneficial in the differentiation of brucellosis from other bacterial infections.

In healthy subjects plasma concentration of PCT is low as picogram level and is under the measurement thresholds of recent methods (<0.1 ng/ml) [12]. In many studies conducted, measurement of serum PCT level is shown to be beneficial in the differentiation of bacterial infections from other inflammatory factors [23]. In our study although the PCT levels were increased in patients in both groups, there was not any statistically significant difference between the two groups (p=0.887). Therefore, we suggest that PCT test can be used in the diagnosis of bacterial infections but PCT will not be beneficial in the differentiation of brucellosis from other bacterial infections. On the other hand, our study is the first in the literature that evaluates the PCT measurement in the patients with brucellosis.

CRP is shown to be beneficial in the diagnosis of acute brucellosis and monitoring the treatment response. However, particularly in the endemic regions it is difficult to differentiate acute, chronic and recurrent infections [13, 24]. In our study, hs-CRP levels were high at both of the study groups. However, hs-CRP levels were found to be significantly higher in the EI group (280±30mg/L)) when compared with the brucellosis group (40±8mg/L (p=0.0001). With these results we suggest that in the diagnosis of brucellosis and bacterial infections and differentiation of these diseases from each other hs-CRP can be used and particularly in extracellular bacterial infections hs-CRP is found to increase to the higher levels. A ROC analysis was performed for diagnosing brucellosis, hs-CRP concentrations equals to 87 mg/L or below this threshold and ESR equals to 22 mm/h or below this value, revealed sensitivities of 92%, 80% and specificities of 74,36%, 76,92%, respectively.

Cakan *et al.* found that the CRP levels are higher in the patients with brucellosis (24.6±27.7mg/L) when compared with the healthy subjects (10.8±21.8 mg/L) (p=0.0001) [13]. Consistently, in two different studies conducted in patients with brucellosis it was shown that 60% of the patients have high levels of CRP [20,21].

In our study, ESR values were higher in the patients at the EI group (40,17±4,52 mm/h) when compared with the patients with brucellosis (16,50±1,75 mm/h) (p=0.0001). While the ratio of the patients that have ESR □ 40 mm/h was 10% in the brucellosis group, patients that have ESR within the range of 20-40 mm/h was found to be 24%.

In the study of Buzgan *et al.* ESR was found to be 20-40 mm/h at the 28,8% of the patients while □40 mm/h at the 20,4% of the patients [19].

Procalcitonin production can be stimulated by bacterial endotoxins, exotoxins and some cytokines. In experimental conditions bacterial endotoxins and TNF-α are the most potent inducers of PCT [12,25]. While Gram negative bacteria are the most frequent causes of urinary system infections, skin-soft tissue infections are frequently caused by gram positive bacteria [26, 27]. In our study PCT values were observed to be higher in the UTI group (0,30±0,11 ng/ml) when compared with the SSTI group (0,04±0,02 ng/ml) as compatible with the literature. This difference was statistically significant (p=0.049). There was not any difference between two groups in terms of NPT and hs-CRP.

In conclusion, it was seen that NPT did not reach to higher levels in brucellosis than extracellular bacterial infections. Also, the likelyhood of detecting increased PCT in brucellosis was not different from that seen in extracellular bacterial infections. On the other hand, ESR and hs-CRP values were found to be different between brucellosis and extracellular bacterial infections although they increased in both infections. ESR and hs-CRP values were higher in patients with extracellular bacterial infections than patients with brucellosis. NPT and PCT elevation is not different in brucellosis from extracellular bacterial infections. However, PCT elevation has been seen to be more marked in UTIs compared to SSTIs. Large scale studies about usefulness of tests such as PCT and NPT are needed.

Acknowledgement

This study was supported by Research Council of Gaziosmanpasa University (No: 2012/17).

Ethical approval: The study protocol was approved by the institutional review board of the Gaziosmanpasa University, Tokat, Turkey (IRB No:11-BADK-044, 2011).

Conflict of Interest: We declare that there is no conflict of interest.

References

[1] Corbel MJ . Brucellosis: an overview. Emerg Infect Dis 1997;3: 213-22.

[2] Coskun O, Oter S, Yaman H, Kilic S, Kurt I, Eyigun CP . Evaluating the validity of serum neopterin and chitotriosidase levels in follow-up brucellosis patients. Intern Med 2010;49(12):1111-8.

[3] Al-Tawfiq JA . Therapeutic options for human brucellosis. Expert Rev Anti Infect Ther. 2008;6(1):109-20.

[4] Colmenero JD, Reguera JM, Fernandez-Nebro A, Cabrera-Franquelo F . Osteoarticular complications of brucellosis. Ann Rheum Dis. 1991;50(1): 23-6.

[5] Kanterewicz E, Sanmarti R, Mellado JA, Euras JM, Brugues J . Pseudogout masking brucellar arthritis. Br J Rheumatol. 1995;34(3): 294-5.

[6] Mert A, Ozaras R, Tabak F, Bilir M, Yilmaz M, Kurt C, et al. The sensitivity and specificity of Brucella agglutination tests. Diagn Microbiol Infect Dis. 2003;46(4):241-3.

[7] Alışkan H . Kultur ve serolojik yontemlerin insan brusellozu tanısındaki değeri. Mikrobiyol Bul. 2008;42(1): 185-95.

[8] Akbulut HH, Celik I, Akbulut A, Yuceb P, Kilic SS . Serum neopterin levels in patients with Brucellosis. J Infect 2005;51, 281–6.

[9] UpToDate. Acute phase reactants. http://www.uptodate.com/contents/acute-phase-reactants? [last accessed July 2013].

[10] Hamerlinck FF . Neopterin: a review. Exp Dermatol 1999;8:167–76.

[11] Diez-Ruiz A, al-Amrani M, Weiss G, Gutierrez-Gea F, Wachter H, Fuchs D . Increased interferon-gamma and neopterin concentrations in patients with acute brucellosis. J Infect Dis 1993;167:504–5.

[12] Meisner M . The prognostic value of PCT. In: Meisner M, editor. Procalcitonin (PCT) — a new, innovative infection parameter. Biochemical and clinical aspects. 2000;pp:63-68, 3rd ed. New York: Thieme.

[13] Gunal O, Ulutan F, Barut Ş . Procalcitonin. Scand J Infect Dis. 2012;44(9):710-1.

[14] Cakan G, Bezirci FB, Kacka A, Cesur S, Aksaray S, Tezeren D, et al . Assessment of diagnostic enzyme-linked immunosorbent assay kit and serological markers in human brucellosis. Jpn J Infect Dis. 2008;61(5):366-70.

[15] Medzhitov R . Origin and physiological roles of inflammation. Nature 2008;454:428.

[16] Vanderschueren S, Deeren D, Knockaert DC, Bobbaers H, Bossuyt X, Peetermans W . Extremely elevated C-reactive protein. Eur J Intern Med 2006;17: 430.

[17] Young EJ . Serologic diagnosis of human brucellosis: analysis of 214 cases by agglutination tests and review of the literature. Rev Infect Dis 1991;13:359–72.

[18] Franco MP, Mulder M, Gilman RH, Smits HL. Human C, Cakcı A . Brusellozda kas iskelet sistemi komplikasyonları. Trakya Üniv Tıp Fak Derg. 2008;25(1): 20-5).

[19] Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, et al . Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis. 2010;14(6):469-678.

[20] Eini P, Keramat F, Hasanzadehhoseinabadi M . Epidemiologic, clinical and laboratory findings of patients with brucellosis in hamadan, west of iran. J Res Health Sci. 2012;12(2):105-8.

[21] Hasanjani Roushan MR, Mohrez M, Smailnejad Gangi SM, Soleimani- Amiri MJ, Hajiahmadi M. Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran. Epidemiol Infect. 2004;132:1109-14.

[22] Haddadi A, Rasoulinejad M, Afhami SH, Mohraz M . Epidemiological, clinical, para clinical aspects of brucellosis in Imam Khomeini and Sina Hospital of Tehran (1998-2005). Behbood Journal. 2006;10:242-51.

[23] Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K . The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection 2008;36: 396 – 407.

[24] Navarro JM, Mendoza J, Leiva J, Rodríguez-Contreras R, de la Rosa M . C-reactive protein as a prognostic indicator in acute brucellosis. Diagn Microbiol Infect Dis. 1990;3:269-70.

[25] Maruna P, Nedelnikova K, Gürlich R . Physiology and genetics of procalcitonin. Physiol Res 2000;49: 57-6.

[26] Stam WE . Urinary Tract Infections, Pyelonephritis and Prostatitis In: Harrison's Infectious Diseadse. Kasper DL, Fauci AS (Eds). 2010;pp:272-283, 17th ed. New York. Mc Graw Hill .

[27] Stevens DL . Infections of the Skin, Muscle and Soft Tissues. In: Harrison's Infectious Diseadse. Kasper DL, Fauci AS (Eds). 2010;pp:230-237, 17th ed. New York. Mc Graw Hill .