



Neopterin, Interleukin-6, Procalcitonin, C-reactive protein and PET-CT staining as markers in infected total knee prosthesis, a retrospective analysis

Koçturk YILDIRIM, Abdulhamit MISIR, Turan Bilge KIZKAPAN, Mustafa OZCAMDALLI, Fuat DUYGULU

From the Gaziantep Dr Ersin Aslan Training and Research Hospital, Turkey

Diagnosis in prosthetic joint infections is challenging as symptoms are variable, and currently most of the diagnostic tests are non-specific. Normal inflammatory reactions after orthopedic prosthetic surgery may generate false positives, as these tests have high sensitivity but low specificity. Thus, specific tests, as alpha defensin, are needed to distinguish bacterial infections from reactions to surgical trauma. The aim of this study was to determine the sensitivity and specificity of several diagnostic tools for detecting bacterial infection in prostheses.

Between April 2010 and December 2012, we analyzed white blood cell count, erythrocyte sedimentation rate, C-reactive protein, neopterin, interleukin-6, and procalcitonin in 45 patients with prosthetic infection confirmed by positive cultures of joint aspirate and deep tissue biopsy. In addition, these patients underwent PET-CT imaging, in accordance with infection protocols in place at our clinic. The suitability and diagnostic power of these tests were assessed by using Shapiro-Wilk test, Mann-Whitney U test, and ROC curve analysis, and by comparing to 40 age- and gender-matched volunteers who underwent unilateral total knee prosthesis with normal serum indices and without known diseases.

Significant differences were observed between infected patients and control volunteers ($p < 0.05$) for all parameters examined. Highest sensitivity (99%) and specificity (98%) were achieved using a combination of interleukin-6 and C-reactive protein. However, PET-CT imaging had diagnostic accuracy of 93.3%.

A combination of interleukin-6 and C-reactive protein also enables accurate diagnosis. PET-CT may be an important imaging modality for detecting prosthesis infection. But, these markers were found neither sensitive nor specific in the diagnosis of periprosthetic infection as alpha defensin.

Keywords : interleukin-6 ; neopterin ; PET-CT ; procalcitonin ; prosthesis infection.

INTRODUCTION

The number of patients who undergo total knee and hip arthroplasty has grown along with the extension of life span and aging of the population. Today, approximately 700,000 knee replacement procedures are performed annually in the US

■ Koçturk Yildirim¹.

■ Abdulhamit Misir².

■ Turan Bilge Kizkapan².

■ Mustafa Ozcamdalli³.

■ Fuat Duygulu⁴.

¹Gaziantep Dr Ersin Aslan Training and Research Hospital, Turkey.

²Baltalimani Bone and Joint Diseases Training and Research Hospital, Turkey.

³Ahi Evran University, Training and Research Hospital Turkey.

⁴Kayseri Training and Research Hospital, Turkey.

Correspondence : Koçturk Yildirim, M.D., Gaziantep Dr Ersin Aslan Training and Research Hospital, Turkey.

E-mail : yildirimkoçturk@gmail.com

© 2018 Acta Orthopaedica Belgica.

No benefits or funds were received in support of this study. The authors report no conflict of interests.

alone. This is projected to increase to 3.48 million procedures a year by 2030 (15). Usually the incidence of infections in TKA is reported to be higher than THA (4). The incidence is on the rise, despite all present prophylactic matters. With advances in surgical techniques, prosthesis design, and preoperative prophylaxis regimens, infection rates have decreased to 1 % for hip and 0.7 % for knee prostheses (4), but remain a serious and potentially fatal issue. Diagnosis is challenging, as symptoms are variable, and current diagnostic tests, including white blood cell count, erythrocyte sedimentation rate, C-reactive protein, scintigraphy, and others, are non-specific (31). Indeed, normal inflammatory reactions after orthopedic prosthetic surgery may generate false positives, as these tests have high sensitivity but low specificity (13). Thus, specific tests are needed to distinguish bacterial infections from reactions to surgical trauma.

The aim of this study was to evaluate the suitability PET-CT imaging, serum C-reactive protein, interleukin-6, neopterin, and procalcitonin as diagnostic tools for detecting prosthesis infection.

MATERIALS AND METHODS

Between April 2010 and December 2012, we enrolled 45 consecutive patients with confirmed periprosthetic joint infection. Infection was confirmed by MSIS criteria for periprosthetic joint infections (Table 1) (8).

The patient population consisted of 39 females and 6 males between 57 and 84 years, with mean age 68.2 (\pm 13.1). All patients had received total knee replacement due to primary osteoarthritis. The mean interval between surgery and periprosthetic joint infection was 4 ± 1.7 years, with range 1.5-12 years. All patients was hospitalized for two-stage revision knee arthroplasty after infection was confirmed. None of the patients treated with antibiotics between first admission and first stage revision. Before the first stage revision, deep tissue biopsy cultures were obtained, all of which tested positive. Blood samples were then collected and tested for neopterin, interleukin-6, procalcitonin, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein. Finally, patients

underwent PET-CT imaging, AP, and lateral X-rays. To determine the normal range for the tested serum indices, samples were also obtained from 40 age- and gender-matched volunteers.

Informed consent was obtained from all infected patients and control volunteers. Patients were excluded based on the following criteria, to prevent other inflammatory and infectious conditions from confounding results: (1) known history of autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, and others; (2) HIV infection; (3) mycobacterial infection; (4) known chronic infectious disease; (5) ongoing immunosuppressive therapy; (6) active dental or urinary tract infection; (7) surgery within the last year.

Study plan

Blood samples (20 cc) were collected, and protected from light. Synovial fluid and serum white blood cell count, serum erythrocyte sedimentation rate, and serum C-reactive protein were measured on the same day. Samples to be tested for neopterin, procalcitonin, and interleukin-6 were aliquoted into different tubes, centrifuged for 10 min at 4,000 rpm, and stored at -70 °C until analyzed by a trained clinical biochemist. Procalcitonin, neopterin, and interleukin-6 were measured on a Tecan-Sunrise microplate reader using, respectively, the ELISA kits ab100630, EIA- 1476 (DRG instrument GmbH, Germany), and EK-0410 (Boster Biological Technology Co., Ltd. Pleasanton, CA, USA).

Pet-CT imaging

Patients received 0.1 mCi/kg ^{18}F -fludeoxyglucose by intravenous injection after fasting for 6 h, and underwent PET-CT imaging 1 h thereafter.

Statistical analysis

Data were analyzed in SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA) and Medcalc 8.1.1.0 for Windows (MedCalc Software BVBA, Ostend, Belgium). A p value < 0.05 was considered statistically significant. The distribution of quantitative variables was evaluated by Shapiro-

Table I.— MSIS PJI infection criteria

One of the following must be met for diagnosis of PJI:	
1)	A sinus tract communicating with the prosthesis
2)	A pathogen is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint
3)	Four of the following six criteria exist:
a)	Elevated ESR and CRP (ESR>30 mm/hour; CRP>10 mg/L)
b)	Elevated synovial fluid WBC count (>3000 cells/microliter)
c)	Elevated synovial fluid neutrophil percentage (>65%)
d)	Presence of purulence in the affected joint
e)	Isolation of a microorganism in one periprosthetic tissue or fluid culture
f)	>5 neutrophils per high-powered field in 5 high power fields observed from histologic analysis of periprosthetic tissue at x400 magnification
ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell	

Wilk test, and normally distributed data were compared between patients and controls by Mann-Whitney U test. Categorical variables were compared using the exact method of the χ^2 test. ROC analysis was used to assess the suitability of biochemical indices as diagnostic tools.

RESULTS

We compared select serum indices between 40 healthy volunteers and 45 patients with confirmed periprosthetic knee infection. All patients had previously undergone total knee arthroplasty, and received two-stage revision knee arthroplasty after infection. Patient and control cohorts were comparable in age and sex ($p > 0.05$). Patients included 39 females (86.7%) and 6 males (13.3%), with mean age 68.2 (± 13.1). Control volunteers consisted of 36 females (90%) and 4 males (10%) with mean age 67 (± 7.1).

Staphylococcus aureus was the most common infecting species, and was detected in deep-tissue

cultures from twenty-four patients (53.3%). Nine patients (20%) were infected with coagulase-negative *Staphylococci*, six patients (13.3%) were infected with *S. epidermidis*. *Acinetobacter* spp. and *Enterococcus faecalis* were detected in three patients (6.7%) each. There was no correlation between laboratory markers and infecting species.

There were significant differences between patients and healthy controls in routine biochemical markers (white blood cell count, erythrocyte sedimentation rate, and C-reactive protein), as well as in interleukin-6, procalcitonin, and neopterin, which are sensitive and specific markers of infection ($p < 0.05$, Table 2).

In ROC analysis, erythrocyte sedimentation rate was 88% sensitive and 81% specific as a marker of infection, with values above 19 mm/hr considered to indicate infection. Similarly, white blood cell count was 77% sensitive and 70% specific, with cut-off value 6,960 cells/ μ l. The sensitivity and specificity values for interleukin-6 were 95% and 96%, respectively, with cut-off at 6.6 pg/ml. For

Table II.— Routine biochemical indices and markers of infection in infected patients and healthy controls.

	CONTROL GROUP (n=40)	PATIENT GROUP (n=45)	P Value
WBC (1000/ μ l)	5,343 \pm 1,006	9,047 \pm 1,614	< 0.001
ESH (mm/saat)	12,6 \pm 4,4	66,7 \pm 26	< 0.001
IL-6 (pg/ml)	3,37 \pm 1,5	82 \pm 31	< 0.001
CRP (mg/L)	3,47 (3,34-4,44)	54 (32-88)	< 0.001
PROCALCITONIN (ng/ml)	0,04 (0,03-0,06)	0,288 (0,158-0,536)	< 0.001
NEOPTERIN (nmol/L)	45,37 \pm 6,5	22,15 \pm 5,3	<0.001

C-reactive protein, the cut-off value was 8.83 mg/l, with sensitivity 95% and specificity 90%. The cut-off value for procalcitonin was 0.081 ng/ml, and this marker was 8% sensitive and 60% specific. The cut-off value, sensitivity, and specificity for neopterin were 32.21 nmol/l, 76%, and 61%, respectively (Table III).

Based on this analysis, the most sensitive and specific test was interleukin-6. C-reactive protein was as sensitive as interleukin 6, but not as specific. Notably, the combination of C-reactive protein and interleukin-6 had 99 % sensitivity and 98 % specificity. On the other hand, procalcitonin and neopterin were the least sensitive and specific (Table III).

Table III.— Sensitivity and specificity of selected biochemical markers in prosthetic infection.

TEST	SENSITIVITY	SPECIFICITY
- WBC	77%	70%
- ESH	88%	81%
- CRP	95%	90%
- IL-6	95%	96%
PROCALCITONIN	80%	60%
NEOPTERIN	76%	61%
IL-6 and CRP	99%	98%

Further, we found that PET-CT imaging detected infection in 42 of 45 patients, based on the accumulation of fludeoxyglucose at the interface between bone and prosthesis. Thus, the sensitivity for PET-CT was deemed to be 93.3 %.

DISCUSSION

Several laboratory parameters, including white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and others, are currently used to diagnose prosthesis infection. However, most of these indices are not specific, and may be elevated after prosthetic surgery even in the absence of infection (23). Medical history, physical, and radiological examination (Ultrasound, CT, and MRG) have similarly low specificity (20).

In particular, Bottner et al. (2) reported normal white blood cell count ($\leq 6,300/\mu$ l) in 14 of 21 infected patients. Similarly, Toossi et al. (26) concluded that serum white blood cell count and differential were uninformative in patients with suspected infection of the prosthetic joint. In line with these results, we found that white blood cell count had sensitivity and specificity of 77 % and 70 %, respectively. Nevertheless, we note that Deirmengian et al. (5) demonstrated that neutrophils in the synovial fluid of an infected knee prosthesis has a gene expression signature distinct from neutrophils in an aseptic knee.

Procalcitonin is induced in response to endotoxins, exotoxins, and some cytokines, of which the most potent are bacterial endotoxins and TNF- α (18). Indeed, endotoxin injection induces a peak in TNF- α and interleukin-6 at 90 and 180 minutes, respectively, followed by an increase in procalcitonin 3-6 hours later. Procalcitonin peaks at 6-8 hours, while C-reactive protein may remain unchanged in the first 6 hours. Accordingly, interleukin-6 and procalcitonin decrease before

C-reactive protein (2,3,19). Bottner et al. (2) reported 98 % specificity for procalcitonin, and concluded that this marker may be clinically useful. In contrast, Drago et al. (12) concluded that procalcitonin is not a good marker of periprosthetic infection. In this study, we found that procalcitonin was significantly different between infected patient and healthy controls, even though mean values remained within normal limits. We determined that the sensitivity and specificity of procalcitonin were 85 % and 60 %.

Neopterin is produced from monocytes and macrophage cells in response to interferon- γ , and is a marker of activated T lymphocytes and cell-mediated immune response (21). In particular, neopterin secretion starts three days before peak T cell proliferation and six days before secretion of specific antibodies. Thus, the molecule is an early marker of infection (14). Indeed, the molecule is elevated during viral infections, severe bacterial infections, and intracellular bacterial infections (10), although higher levels of neopterin and of C-reactive protein were noted in bacterial infection than in viral infection (24). Accordingly, we detected elevated levels of neopterin in infected patients, with sensitivity 76 % and specificity 61 % at levels above 32.21 nmol/l. We note that serum neopterin varies with age, but not with sex (28), and is highest in children and the elderly. In particular, the mean serum level is 5.5 ± 2.7 nmol/l between 19 and 75 years, and 10 ± 5 nmol/l above 75 years.

C-reactive protein is the most common test used to diagnose prosthetic infections, even though Bottner et al. (2) reported normal levels in some infected patients and sensitivity values below 95 %. We found C-reactive protein to be the second most sensitive (95 %) and specific (90 %) laboratory marker of prosthesis infection after interleukin-6. In addition, we found that C-reactive protein was not significantly different between obese and non-obese patients ($p > 0.05$), in contrast to Liu et al. (16), who proposed higher cut-off values for obese patients.

Combining C-reactive protein with other laboratory tests may also be clinically useful. For example, Spangehl et al. (25) reported strong diagnostic value for a combination of C-reactive

protein and erythrocyte sedimentation rate in 178 patients with infected total hip arthroplasty, even though erythrocyte sedimentation rate alone was uninformative. Thus, we propose that a combination of erythrocyte sedimentation rate > 30 mm/hr and C-reactive protein > 10 mg/L should raise suspicion of prosthetic infection.

However, interleukin-6 was found to have stronger diagnostic value than erythrocyte sedimentation rate and C-reactive protein. In addition, interleukin-6 returns to baseline 48-72 hours after surgery, and thus would be a useful marker in the early postoperative phase (29). Di Cesare et al. (11) found that interleukin-6 levels > 10 pg/ml were adequately sensitive and specific, although levels may be similarly elevated in patients with polyethylene wear and osteolysis. In addition, Bottner et al. (2) reported that a combination of interleukin-6 above 12 pg/ml and C-reactive protein higher than 3.2 mg/dl had the highest sensitivity and specificity. In our study, interleukin-6 and C-reactive protein were similarly sensitive and specific. In particular, we found 95 % sensitivity and 96 % specificity for interleukin-6 above 6.6 pg/ml, as well as 95 % sensitivity and 90 % specificity for C-reactive protein beyond 8.83 mg/l. Combination of these two markers further increased sensitivity and specificity to 99 % and 98 %. Thus, we recommend that a combination of interleukin-6 and C-reactive protein be used as a test for prosthetic infection. Unfortunately, we are unable to comment on the impact of aseptic loosening on these markers.

Alpha-defensin peptide has been demonstrated to be an accurate proxy for the definition of PJI. Bingham et al. (1) reported 100% sensitivity and 95% specificity for Alpha defensin-1. And they concluded the sensitivity and specificity of the synovial fluid AD-1 assay exceeded the sensitivity and specificity of the other currently available clinical tests evaluated in their study but did not reach significance. Also, Deirmengian et al. (6) demonstrated 100% sensitivity and specificity of synovial fluid alpha defensin with a novel synovial fluid optimized immunoassay in the diagnosis of PJI. In the same study they evaluated Leukocyte esterase strips and found 69% sensitivity and

100% specificity. Also, Deirmengian et al. (7) demonstrated a sensitivity of 97% and a specificity of 100% with synovial fluid alpha defensin and CRP combination for the diagnosis of periprosthetic joint infection. This was achieved despite the inclusion of patients with systemic inflammatory disease and those receiving treatment with antibiotics. They stated that future research should focus on the performance of this test in specific clinical scenarios such as the immediate postoperative period in the setting of severe immunocompromise and in the setting of a native joint. We found lower sensitivity and specificity of all biomarkers evaluated in this study than synovial fluid alpha defensin.

There are two main opinions in the literature on the diagnostic value of PET-CT imaging in cases of prosthetic infection. On one hand, pharmaceutical PET-CT imaging is recommended to rule out aseptic loosening. On the other, fludeoxyglucose staining at the interface between bone and prosthesis is considered to indicate septic loosening (13). However, Zhuang et al. (30) reported persistent fludeoxyglucose staining in the first postoperative year in approximately 63 % of femoral components and in 89 % of tibial components, suggesting that PET-CT imaging may generate false positives during this period. We note, however, that all patients in this study were postoperative for at least 1.5 years.

Fludeoxyglucose, a marker of glucose metabolism, visualizes generic inflammation, and is probably less specific than other imaging modalities. A potential alternative is combined leukocyte scintigraphy, which visualizes leucocyte migration and has high specificity for infected prosthesis (27), and more than 90 % accuracy (17). However, combined leukocyte scintigraphy is time-consuming, requires processing of blood products, and is affected by antibiotic treatments. In a side-by-side comparison in 89 patients with infected hip arthroplasty, leukocyte combined scintigraphy was found to have 50 % sensitivity and 95.1 % specificity, while fludeoxyglucose PET-CT had sensitivity 93 % and specificity 95.2 % (22).

Fludeoxyglucose PET-CT detected 93 % of confirmed cases of prosthetic knee infection, in line with published results. However, we were

unable to measure specificity, as volunteers without infection declined to undergo this procedure. Thus, more studies are needed to better characterize the diagnostic value of PET-CT imaging, especially as specificity has been reported to be higher for periprosthetic infections in the hip than in the knee.

CONCLUSION

The current literature shows that synovial alpha defensin has the highest sensitivity and specificity in the diagnosis of PJI. But combination of serum interleukin-6 and C-reactive protein has high sensitivity and specificity as diagnostic markers of prosthetic knee infection. Thus, this combination may be used as a screening test for suspected cases of periprosthetic infection if alpha defensin measurement is not available. PET-CT and alpha defensin measurement are expensive diagnostic modalities. Also, CRP and Interleukin-6 combination enables a cost effective diagnostic screening in the suspicion of PJI.

The main limitation of this prospective study was the relatively small sample size. It is possible that statistically significant differences in selected biochemical and serum indices could be observed in a larger cohort of patients.

REFERENCES

1. Bingham J, Clarke H, Spangehl M, Schwartz A, Beauchamp C, Goldberg B. The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty. *Clin Orthop Relat Res* 2014 ; 472 : 4006-4009.
2. Bottner F, Wegner A, Winkelmann W, Becker K, Erren M, Götze C. Interleukin-6, procalcitonin and TNF-alpha: markers of peri-prosthetic infection following total joint replacement. *J Bone Joint Surg Br* 2007 ; 89 :94-9.
3. Carrol ED, Thomson APJ, Hart CA. Procalcitonin as a marker of sepsis. *Int J Antimicrob Agents* 2002 ; 20 : 1-9.
4. Darouiche R. Treatment of infections associated with surgical implants. *N Engl J Med* 2004 ; 350 : 1422-9.
5. Deirmengian C, Lonner JH, Booth RE Jr. The Mark Coventry Award: white blood cell gene expression: a new approach toward the study and diagnosis of infection. *Clin Orthop Relat Res* 2005 ; 440 : 38-44.
6. Deirmengian C, Kardos K, Kilmartin P et al. The alpha-defensin test for periprosthetic joint infection outperforms the leukocyte esterase test strip. *Clin Orthop Relat Res* 2015 ; 473 : 198-203.

7. **Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J.** Combined measurement of synovial fluid alpha-defensin and c-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. *J Bone Joint Surg Am* 2014 ; 96 : 1439-1445.
8. **Deirmengian C, Kardos K, Kilmartin P, Gulati S, Citrano P, Booth RE Jr.** The Alpha-defensin test for periprosthetic joint infection responds to a wide spectrum of organisms. *Clin Orthop Relat Res* 2015 ; 473 : 2229-35.
9. **Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J.** Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? *Clin Orthop Relat Res* 2014 ; 472 : 3254-62.
10. **Denz H, Fuchs D, Hausen A et al.** Value of urinary neopterin in the differential diagnosis of bacterial and viral infections. *Klin Wochenschr* 1999 ; 68 : 218-22.
11. **Di Cesare PE, Chang E, Preston CF, Liu CJ.** Serum interleukin-6 as a marker of periprosthetic infection following total hip and knee arthroplasty. *J Bone Joint Surg Am* 2005 ; 87 : 1921-7.
12. **Drago L, Vassena C, E et al.** Procalcitonin, C-reactive protein, interleukin-6, and soluble intercellular adhesion-molecule-1 as markers of postoperative orthopaedic joint prosthesis infections. *Int J Immunopathol Pharmacol* 2011 ; 24: 433-40.
13. **Hanssen A D, Rand J A.** Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. *J Bone Joint Surg* 1998 :80-A : 910-922
14. **Hoffmann G, Wirleitner B, Fuchs D.** Potential role of immune system activation-associated production of neopterin derivatives in humans. *Inflamm Res* 2003 ; 52 : 313-21.
15. **Kurtz S, Ong K, Lau E, et al.** Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007 ; 89 : 780.
16. **Liu JZ, Saleh A, Klika AK, Barsoum WK, Higuera CA.** Serum inflammatory markers for periprosthetic knee infection in obese versus non-obese patients. *J Arthroplasty* 2014 ; 29: 1880-3.
17. **Love C, Tomas MB, Marwin SE, Pugliese PV, Palestro CJ.** Role of nuclear medicine in diagnosis of the infected joint replacement. *Radiographics* 2001 ; 21: 1229-38.
18. **Meisner M.** Procalcitonin-a new, innovative infection parameter biochemical and clinical aspects. 3rd revised and expanded ed. Thieme, Stuttgart, New York , 2000, 27-45.
19. **Maruna P, Nedelnikova K, Gürlich R.** Physiology and genetics of procalcitonin. *Physiol Res* 2000 ; 49 : 57-61.
20. **Moran E, Byren I, Atkins BL.** The diagnosis and management of prosthetic joint infections. *J Antimicrob Chemother* 2010 ; 65: iii 45-54.
21. **Murr C, Widner B, Wirleitner B, Fuchs D.** Neopterin as a marker for immun system activation. *Current drug metabolism* 2002 ; 3 : 175-87.
22. **Pill SG, Parvizi J, Tang PH, Garino JP, Nelson C, Zhuang H, et al.** Comparison of fluorodeoxyglucose positron emission tomography and (111) indium-white blood cell imaging in the diagnosis of periprosthetic infection of the hip. *J Arthroplasty* 2006 ; 21: 91-7.
23. **Scherer MA, Neumaier M.** C-reactive protein in patients who had operative fracture treatment. *Clin Orthop Rel Res.* 2001 ; 393 : 287-93.
24. **Shaw AC.** Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. *Clin Pathol* 1991 ; 44 : 596-9.
25. **Spanghel MJ, Masri BA, O'Connell JX, Duncan CP.** Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *J Bone Joint Surg Am* 1999 ; 81: 672-83.
26. **Toossi N, Adeli B, Rasouli MR, Huang R, Parvizi J.** Serum white blood cell count and differential do not have a role in the diagnosis of periprosthetic joint infection. *J Arthroplasty* 2012 ; 27 : 51-4.e1.
27. **Van Acker F, Nuyts J, Maes A, Vanquickenborne B, Stuyck J, Bellemans J, et al.** FDG-PET, 99mTc-HMPAO white blood cell SPET and bone scintigraphy in the evaluation of painful total knee arthroplasties. *Eur J Nucl Med* 2001 ; 28 : 1496-504.
28. **Werner ER, Bichler A, Daxenbichler G, et al.** Determination of neopterin in serum and urine. *Clinical Chemistry* 1987 ; 33: 62-66.
29. **Wirtz DC, Heier KD, Mitter O, Ziikens KW, Woiff JM.** Interleukin-6: a potential inflammatory marker after total joint replacement. *Int Orthop* 2000; 24 : 194-6.
30. **Zhuang H, Chacko TK, Hickeson M, Stevenson K, Feng Q, Ponzo F, et al.** Persistent non-specific FDG uptake on PET imaging following hip arthroplasty. *Eur J Nucl Med Mol Imaging* 2002 ; 29 : 1328-33.
31. **Zimmerli W, Trampuz A, Ochsner P.** Prosthetic-joint infections. *N Engl J Med* 2004 ; 351 : 1645-54.