

Value of D-Dimer as a Diagnostic Marker of Infection Associated with Orthopedic Implants

Abstract

Background: Recently, the D-dimer biomarker has gained the researchers' attention for predicting infections. We aimed to determine the relationship between this marker and other inflammatory markers involved in orthopedic implant-associated infections. **Materials and Methods:** In this study, all patients diagnosed with an orthopedic implant-associated infection were investigated in 3 years. The serum level of D-dimer, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) was measured. Infection was diagnosed based on the clinical and culture results of biopsy samples. **Results:** The cultured microorganisms, detected in 26 patients with infections, included *Staphylococcus aureus* ($n = 13$, 50%), *Staphylococcus epidermidis* ($n = 2$, 7.7%), *Klebsiella aerogenes* ($n = 8$, 30.8%), and *Pseudomonas aeruginosa* ($n = 3$, 11.5%). Based on laboratory findings, there was a significant difference in the CRP level and ESR ($P = 0.001$). Although the level of D-dimer was higher in infected patients, compared to the controls (992.6 ± 667.2 vs. 690.1 ± 250.2 ng/mL), the difference was not statistically significant. There was no significant correlation between the elevated D-dimer level and CRP level, whereas ESR had a positive correlation with the elevated D-dimer level ($r = 0.6$, $P = 0.03$). The sensitivity, specificity, and positive predictive value (PPV) of D-dimer in the prediction of infection were 65%, 57%, and 45%, respectively. Furthermore, the sensitivity, specificity, and PPV of CRP were 100%, 92.3%, and 95%, respectively, whereas the corresponding values for ESR were 85%, 69.2%, and 62%, respectively. **Conclusion:** Measurement of the serum D-dimer level is not efficient for the diagnosis of orthopedic implant-associated infections due to its low predictive value. Furthermore, there was no significant correlation between the serum D-dimer level and CRP.

Keywords: C-reactive protein, D-dimer, erythrocyte sedimentation rate, infection, orthopedic, osteomyelitis

Introduction

Infection is one of the main causes of re-operation and revision surgery following orthopedic procedures, especially those involving hip and knee arthroplasty.^[1] It is the most important cause of treatment failure after revision arthroplasty.^[1,2] The accurate diagnosis of infection following orthopedic surgeries is one of the major clinical challenges.^[3] Currently, there is no definite diagnostic test for prosthetic or implant-associated infections. These infections are often detected via separation of synovial fluid or culture studies of surgical site biopsies.

Based on the Musculoskeletal Infection Society guidelines, the diagnosis of infections caused by orthopedic implants is often based on experimental data.

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The common laboratory markers include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count, neutrophil percentage, and leukocyte esterase test. Experimental studies have shown that the interleukin-6 (IL-6) level is one of the markers of periprosthetic joint infection, which is not routinely measured due to its high cost.^[4]

CRP and ESR are two noninvasive and inexpensive markers for investigating the presence of infections. The increase of these two markers has a significant correlation with infections caused by hip and knee implants.^[4] However, factors other than infection can also increase the level of these two markers. These two inflammatory markers show low sensitivity to infections in orthopedic implant revisions of the spine or shoulder. Moreover, they have a low predictive value and sensitivity in

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diagnosing infections caused by shoulder implants, which can be attributed to the low virulence of the underlying organism (often *Propionibacterium*).^[5] In other orthopedic implants, the underlying microorganisms often include *Staphylococcus aureus* and *Staphylococcus epidermidis*.^[5]

Recent studies have reported the involvement of D-dimer, a common marker of venous thrombosis, in local and systemic infections with increased fibrinolytic activities.^[6] Furthermore, various studies have suggested the increased level of D-dimer as an important factor in predicting the adverse consequences of sepsis and bacteremia.^[6,7] Therefore, in this study, we aimed to investigate the correlation between the D-dimer level and other inflammatory markers in orthopedic infections.

Materials and Methods

This study was conducted from May 2015 to December 2019 in trauma centers located in the northwest of Iran. The study population included 52 patients with a history of fracture in the lower extremities and a possible orthopedic implant-associated infection. In this study, 52 patients with a simple sampling method based on a study of Shahi *et al.*,^[4] and according to the study power of 80% ($Z = 1.96$) with the loss of follow-up of 10% with Minitab 13 software, were included in the study. The exclusion criteria were as follows: (1) having a weak immune system, (2) diagnosis of malignancies, (3) a hypercoagulable disorder, (4) a prosthetic heart valve, (5) systemic inflammatory disorders, (6) inflammatory bowel disease, (7) hepatitis B or hepatitis C, (8) gout and multiple myeloma, (9) lymphocytic leukemia, and (10) diagnosis of myelodysplastic syndromes. Furthermore, patients with a history of antibiotic consumption 1 month before hospitalization and those with possible infections in other organs were excluded. All patients underwent in-depth color Doppler ultrasonography and were excluded in the case of thrombosis. The demographic data, as well as type of initial fracture (open or closed), history of diabetes, smoking, and fracture site, were recorded.

The primary criteria for infection were the presence of sinus tracts, persistent wound drainage, and the onset of the prosthesis or implant-related pain (acute/chronic). Further laboratory investigations were conducted by measuring CRP, ESR, and D-dimer levels by collecting venous blood samples at the time of hospitalization. In this study, ESR >33 mm/h, CRP >10 mg/L, and D-dimer level >850 ng/mL were indicative of a possible infection [Figure 1].^[5] Among 52 patients, with the mean age of 54.5 ± 11.5 years, 6 (11.5%) were excluded due to venous thrombosis symptoms.

Our final investigations, based on the cultured samples and clinical observations during surgery, showed that 26 patients had infections, whereas 20 patients had no implant-associated infections. All patients, who underwent surgery, experienced

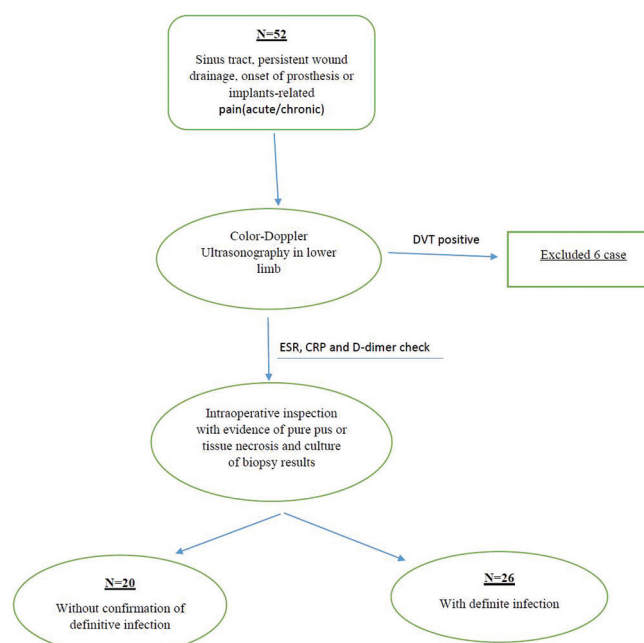


Figure 1: Patients selection. DVT: Deep vein thrombosis, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

irrigation and debridement, and revision surgery was carried out. An intraoperative inspection was performed during surgery, and any evidence of pus confirmed the presence of an infection. Furthermore, three to six biopsy samples were prepared from different parts and sent for culturing. Finally, the patients were divided into two groups of definitely infected and noninfected nonunion.

Statistical analysis was conducted, using Pearson's correlation test to investigate the correlations of experimental results. Furthermore, the specificity and sensitivity of each test were determined. The SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA).was used for all statistical analyses, and $P < 0.05$ was considered statistically significant.

This study was conducted after obtaining informed consent forms from the patients. The Ethics Committee of Urmia University of Medical Sciences (Urmia, Iran) approved this study (code: 1396-09-32-3285).

Results

Among patients with a definite infection, the frequency of cultured microorganisms was as follows: *S. aureus* ($n = 13$, 50%), *S. epidermidis* ($n = 2$, 7.7%), *Klebsiella aerogenes* ($n = 8$, 30.8%), and *Pseudomonas aeruginosa* ($n = 3$, 11.5%). The mean time until the occurrence of infection was 6.8 ± 3.04 months (minimum: 2; maximum: 16). There was no significant difference between the two groups in terms of the demographic characteristics, type of fracture, and possible risk factors [Table 1].

The qualitative comparison of D-dimer level showed no significant difference between the two groups. However, the laboratory results indicated a significant difference between the groups in terms of the serum CRP level and ESR. [Table 2] Although the level of D-dimer was higher in patients with infections, the difference was not statistically significant. The D-dimer and CRP levels had no significant correlation, whereas the D-dimer level had a positive correlation with ESR ($r = 0.6$, $P = 0.03$). The sensitivity, specificity, and positive predictive value (PPV) of D-dimer in the prediction of infection were 65%, 57%, and 45%, respectively. Furthermore, the sensitivity, specificity, and PPV of CRP were 100%, 92.3%, and 95%, respectively, whereas the corresponding values for ESR were 85%, 69.2%, and 62%, respectively.

Discussion

CRP is one of the acute-phase reactants produced in the liver in response to inflammation. It is often used for monitoring response to treatment in chronic inflammatory diseases, such as rheumatoid arthritis.^[8] It is also one of the major biomarkers in chronic infections, with a higher predictive value than other biomarkers. It is widely used due to its high accessibility and repeatability, besides low cost. In this regard, Ugarte *et al.* measured the serum concentration of CRP in 111 patients with infection and septicemia and compared it with 79 healthy controls; the results indicated a significant increase in the CRP level. The mean level of this biomarker was 12 mg/dL in patients with

infection versus 5.6 mg/dL in normal controls. Overall, a serum CRP level >7.9 mg/dL had a high predictive value.^[9] However, in 33% of patients with no definite infection, the serum level of this biomarker was 7.9 mg/dL, which made it difficult to detect infections.

Moreover, in studies by Reny *et al.* and Póvoa *et al.*, the serum level variations of CRP over 4 days of hospitalization were considered a strong risk factor for infection. CRP measurements can also improve the recovery of patients during treatment.^[10,11] The results reported by Póvoa *et al.* also suggested a positive correlation between the CRP level and the severity of infection. In this study, the cutoff point was approximately 8.7 mg/dL; in other words, values exceeding this point indicated the high risk of infection. The sensitivity and specificity of CRP were also determined to be 93.4 and 86.1 mg/dL, respectively. Furthermore, when other signs of systemic infection, such as high body temperature (38.2°C), are considered, the diagnosis sensitivity can reach as high as 100%.^[12] In similar findings of our study, CRP was a high sensitive biomarker in determination of infection related to the implants. Infection and septicemia can damage the hemostasis system and increase disseminated intravenous coagulation. D-dimer can increase fibrin degradation following fibrinolysis.^[13] In 1990, D-dimer was recognized as a bacteremia factor in septicemia patients and showed a significant correlation with the severity of septicemia.^[14] In the most recent study conducted in 2017 by Shahi *et al.*, the role of D-dimer in the diagnosis of knee arthroplasty-induced infection was assessed. In this cohort study, a total of 245 patients with initial arthroplasty, 23 patients with revision surgery, and 86 cases of aseptic failure were investigated. The level of D-dimer, CRP, and ESR was monitored for all patients. The results indicated the high sensitivity of serum D-dimer level in the diagnosis of infection ($P = 0.001$); the optimal threshold for the serum level of D-dimer was 850 ng/mL. Moreover, the sensitivity of D-dimer, ESR, and CRP was 89%, 73%, and 78%, respectively, with specificities of 93%, 79%, and 80%, respectively. According to this study, D-dimer is a powerful marker for diagnosing knee arthroplasty-induced infections.^[4]

Moreover, Shahi *et al.* found that D-dimer, in combination with ESR and CRP, had a high diagnostic value for periprosthetic joint infection (joint arthroplasty). Among five patients with increased D-dimer levels (>850 ng/dL), the ESR and CRP levels were normal in two patients, and they only had a high D-dimer level, according to the positive culture. Therefore, an increase in D-dimer level is the only marker of low-grade infection, associated with high sensitivity and specificity.^[4]

In a study by Piper *et al.*, the correlation between ESR and CRP was investigated in 636 patients, undergoing orthopedic implant surgeries, including 297 knee and 221 shoulder surgeries. Based on their results, ESR >53.5 mm/h

Table 1: Demographic findings and qualitative measurement of D-dimer between two groups

Variable	Patients with infection (n=26), n (%)	Patients without infection (n=20), n (%)	P
Sex (male/female)	15 (57.7)/11 (42.3)	13 (65)/7 (35)	0.4
Age (years)	54.03±11.2	51.2±11.9	0.5
Patients with diabetes	10 (38.5)	5 (25)	0.1
Smoking consumption	7 (26.9)	6 (30)	0.5
D-dimer positive (>850 ng/ml)	15 (57.7)	7 (35)	0.1
Tibial fractures	19 (73.1)	12 (60)	0.4
Femoral fractures	7 (26.9)	8 (40)	0.2
Closed fractures	20 (62.5)	12 (37.5)	0.1
Open fractures	6 (42.9)	8 (57.1)	

Table 2: Comparison of laboratory findings between two groups

Variable	Patients with infection (n=26)	Patients without infection (n=20)	P
CRP (mg/d)	29.1±14.2	7.3±1.3	0.001*
ESR (mm/h)	45.5±20.7	24.3±9.6	0.03*
D-Dimer (ng/ml)	992.6±667.2	690.1±250.2	0.06

*Significant difference. CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

had a significant correlation with a knee infection. The cutoff points of ESR for knee, hip, shoulder, and spine surgeries were 19, 12, 26, and 45 mm/h, respectively. Based on these cutoff points, the sensitivity and specificity of ESR in the diagnosis of infection were 89% and 74% for knee, 82% and 60% for hip, 32% and 93% for shoulder, and 54% and 90% for spine surgeries, respectively. In this study, CRP was also used to detect knee and hip infections, with a cutoff value of 52 mg/dL. Its sensitivity was estimated at 88%, 74%, 63%, and 79% for knee, hip, shoulder, and spine surgeries, respectively, with specificities of 79%, 79%, 73%, and 68%, respectively. Based on this study, ESR and CRP had low sensitivity in detecting chronic infections caused by shoulder and spine orthopedic surgeries.^[5] Contrary to their findings in our study, CRP was a high sensitive biomarker compared to the D-dimer in prediction of infection related to the implants.

In the present study, there was no significant correlation between the increased serum level of D-dimer and CRP, while there was a positive correlation between the serum level of D-dimer and ESR. D-dimer also exhibited low sensitivity and specificity in detecting possible infections. In two cases of infection due to Gram-negative organisms (*Klebsiella*), the measured CRP level was <10 mg/dL, and the D-dimer level was <820 ng/dL. The results showed that D-dimer has a low predictive value for detecting infections associated with long bone implants, unlike periprosthetic joint infections. Therefore, an elevated D-dimer level cannot be used in the diagnosis of these infections.

One of the reasons for the difference between the two mentioned studies can be the effect of the infection mechanism on the production of related inflammatory markers. An inflamed synovium secretes high levels of fibrin, whose degradation results in the increased level of D-dimer in the serum and synovial fluid.^[15-21] Previous studies have shown that numerous coagulation factors can cause pro-inflammatory effects following the coagulation cascade.^[15] The expression of inducible tissue factors in endothelial cells and monocytes, and consequently, accumulation of pro-inflammatory factors, such as cytokines (IL-1 and IL-6) and tumor necrosis factor, may also occur.^[16-20]

Various studies have shown that fibrinogen (fibrin) can increment inflammatory responses. In this regard, Ribera *et al.* showed an increase in the synovial fluid D-dimer level in infections due to septic arthritis.^[21] Moreover, increased fibrinolytic activities, production of coagulation products, and elevated D-dimer level are associated with infection localization to prevent systemic injuries. Therefore, the difference between our study and previous research can be attributed to the mentioned mechanism. In the present study, we measured the serum D-dimer level in patients with implant-induced infections of long bones and due to

no synovial tissue there was not creating an inflammatory cascade and producing D-dimer. Therefore, measurement of the serum D-dimer level is not applicable for detecting infections caused by implants for fractures, and the serum CRP level can be determined in these patients.

Limitation of study

In our study, there were no measured levels of IL, especially IL-6. Comparison of ILs with our studied biomarkers, which could help determine more accurate biomarkers. The patients we studied were traumatic, and various factors could play a role in causing the infection. This is despite the fact that in studies on joint replacement infections, patients are more matched.

Conclusion

Based on the present results, the measurement of serum D-dimer level is not effective in detecting orthopedic implant-associated infections, given its low predictive value. Furthermore, no significant correlation was observed between this biomarker and other inflammatory markers such as CRP, however, there was a weak correlation with ESR level.

Ethical Issues

The study was confirmed by the Ethics Committee of Urmia University of Medical Sciences.

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Conflicts of interest

There are no conflicts of interest.

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