Ann Med Res 2020;27(4):1077-81

Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.11.694

Original Article

The role of inflammatory markers in the diagnosis and follow-up of diabetic foot osteomyelitis

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Abstract

Aim: Diabetic foot infections are a major cause of mortality and morbidity in diabetic patients. These mortality and mortality rates increase further when osteomyelitis develops. Simple techniques are needed to facilitate the diagnosis and follow-up of diabetic foot osteomyelitis.

Material and Methods: Eighty-nine patients who underwent amputation due to diabetic foot between January 2012 and May 2017 were included in the study. The patients were grouped as those with or without osteomyelitis according to their pathology results. C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were assessed pre- and postoperatively.

Results: Preoperative ESR values were significantly higher in the osteomyelitis group ($p<0.05$), but there was no statistically difference in CRP ($p>0.05$). Comparison of preoperative, postoperative 2-week, and postoperative 1-month ESR values showed a statistical difference among all time points ($p<0.05$), with lower postoperative values compared to preoperative values. At a cut-off value of 55.5 mm/h, preoperative ESR had sensitivity of 95.3% and specificity of 87.5% in the discrimination of patients with and without osteomyelitis.

Conclusion: ESR is a simple, rapid, and cost-effective diagnostic marker with high sensitivity and specificity in the diagnosis of diabetic foot osteomyelitis. However, monitoring CRP values may be superior to ESR when evaluating early treatment response.

Keywords: C-reactive protein; diabetic foot infections; erythrocyte sedimentation rate; osteomyelitis

INTRODUCTION

Diabetic foot infections are one of the most frequent complications of diabetes and are a leading cause of hospitalization and nontraumatic foot amputation in people with diabetes (1). Osteomyelitis is one of the most common complications of diabetic foot ulcer and infections, occurring in 20 to 60% of cases, depending on the underlying infection (2).

Osteomyelitis and prolonged treatment duration are associated with higher rates of morbidity, mortality, and need for amputation in patients with diabetes. Therefore, early diagnosis and treatment of diabetic foot osteomyelitis is crucial. However, diagnosing osteomyelitis is particularly difficult in the early stages. Diagnostic imaging modalities such as labeled-leukocyte bone scintigraphy and magnetic resonance imaging (MRI) have high sensitivity and low specificity, in addition to being costly. Bone biopsy is considered the gold standard in the diagnosis of osteomyelitis. However, less invasive biochemical parameters may also provide strong evidence regarding the presence of osteomyelitis. Elevated levels of serum inflammatory markers have been observed in diabetic foot osteomyelitis (3).

In this study, we evaluated the inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level in patients who underwent large, intermediate, and small bone amputations in our center due to diabetic foot injury.

MATERIAL and METHODS

Eighty-nine patients who underwent finger, transmetatarsal, and transtibial amputations due to diabetic foot injury in the Department of Plastic, Reconstructive and Aesthetic Surgery at Cumhuriyet University Medical Faculty between January 2012 and May 2017 were included in the study. Data were collected from the patients' files in the automated hospital records system and their pathology reports. The patients were analyzed according to sex, age, type of amputation, and whether pathology results indicated osteomyelitis. The patients were then divided into two groups according

Received: 04.11.2019 **Accepted:** 07.01.2020 **Available online:** 26.03.2020
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to their pathology findings: patients with osteomyelitis (osteomyelitis group) and those without osteomyelitis (control group). ESR and CRP values were assessed preoperatively (within 3 days before surgery) and at postoperative 2 weeks and 1 month. The study was approved by the Cumhuriyet University Ethics Committee.

Statistical Analysis

ESR and CRP values of the patients in the osteomyelitis and control groups were evaluated separately using Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent-samples t-test was used with normally distributed variables and Mann–Whitney U test was used with non-normally distributed variables. When comparing preoperative and postoperative values, the ESR and CRP values of the patients were assessed separately with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Unpaired t test was used for values showing normal distribution, while Wilcoxon test was used for those not showing normal distribution. The association between patient age and their ESR and CRP values was evaluated with Spearman correlation test. Screening tests (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) and receiver operating characteristic (ROC) curve analysis were used to determine the positive limit value (cut-off). Confidence level was set to 95% in all analyses. The data were analyzed using SPSS 23.0 package software.

RESULTS

A total of 97 patients underwent amputation due to diabetic foot injury between January 2012 and May 2017. Of these, 8 patients were excluded due to lack of pathology results and/or CRP or ESR data. Of the 89 patients included in our study, 66.3% (n=59) were men and 33.7% (n=30) were women and the mean age was 64.7 ± 9 years (Table 1). Most of the patients (80.8%, n=72) underwent finger amputation, 6.74% (n=6) underwent transmetatarsal amputation, and 11.2% (n=10) underwent transtibial amputation. Osteomyelitis was detected histopathologically in 73% (n=65) of the patients, whereas no findings suggestive of osteomyelitis were noted in 27% (n=24). Preoperative ESR and CRP values of the patients are shown in Table 2.

Table 1. ESR and CRP Values

		Number of patient	Minimum value	Maximum value	Mean value
Preoperative ESH *(mm/hour)*	Osteomyelitis	65	49	150	86 ±22
	Control	24	11	88	43 ±17
Preoperative CRP *(mg/dl)*	Osteomyelitis	65	5	283	95 ±76
	Control	24	40	156	85 ±27
Postoperative 2nd week ESH *(mm/hour)*	Osteomyelitis	65	18	137	71 ±28
	Control	24	11	68	37 ±13
Postoperative 2nd week CRP *(mg/dl)*	Osteomyelitis	65	3	130	39 ±31
	Control	24	10	72	29 ±12
Postoperatif 1st month ESH *(mm/hour)*	Osteomyelitis	65	4	110	50 ±21
	Control	24	8	62	33 ±12
Postoperatif 1st month CRP *(mg/dl)*	Osteomyelitis	65	2	202	22 ±27
	Control	24	5	21	12 ±5

Table 2. The decrease percentage of postoperative ESR and CRP values

		Minimum	Maximum	Mean	Standard Deviation	p
A for ESR	Osteomyelitis	-77.22	96.84	-16.80	26.63	0.106
	Control	-22.73	0.00	-11.09	6.48	
B for ESR	Osteomyelitis	-96.46	31.03	-39.40	24.04	<0.001
	Control	-47.06	-7.14	-22.84	9.24	
C for ESR	Osteomyelitis	-96.26	25.35	-25.62	22.91	0.001
	Control	-35.71	-4.88	-13.22	8.45	
A for CRP	Osteomyelitis	-93.48	244.44	-42.71	48.01	0.004
	Control	-79.07	-44.83	-65.25	9.64	
B for CRP	Osteomyelitis	-98.94	688.89	-56.92	97.67	<0.001
	Control	-95.31	-63.79	-85.38	7.22	
C for CRP	Osteomyelitis	-86.67	405.00	-34.79	65.86	0.030
	Control	-81.94	-33.33	-57.45	15.97	

A: The decrease percentage of postoperative 2nd week value as per preoperative valeu(%)
B: The decrease percentage of postoperative 1st month value as per preoperative valeu(%)
C: The decrease percentage of postoperative 2nd week value as per preoperative valeu(%)

Preoperative ESR values were significantly higher in the osteomyelitis group compared to the control group ($p<0.05$). There was no statistical difference between the groups in preoperative CRP values ($p>0.05$).

Comparison of preoperative, postoperative 2-week, and postoperative 1-month ESR and CRP values in the osteomyelitis group revealed statistically significant differences among the time points ($p<0.05$), with postoperative values lower than preoperative values. Similarly, there were significant differences in the ESR and CRP values of the control group among the time points ($p<0.05$), with postoperative values lower than preoperative values.

Percentage decreases in postoperative ESR and CRP values relative to preoperative values are shown in figure 1, 2. When the decreases between preoperative and postoperative ESR and CRP values in the control and osteomyelitis groups were compared, the decrease in ESR at postoperative 2 weeks was not significant ($p<0.05$), while the decreases at all other time points were found to be statistically significant ($p<0.05$).

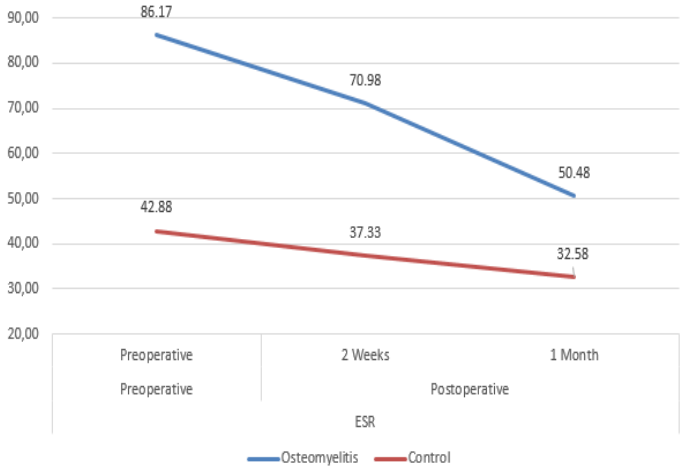

Figure 1. Preoperative and postoperative erythrocyte sedimentation rate (ESR) in the osteomyelitis and control groups

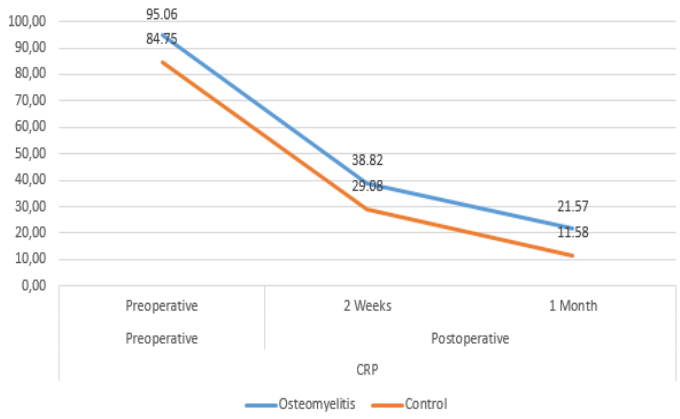

Figure 2. Preoperative and postoperative C-reactive protein (CRP) values in the osteomyelitis and control groups

Due to the significant difference in preoperative ESR values between the osteomyelitis and control groups in our study, the sensitivity, specificity, PPV, and NPV were calculated for different ESR values (60, 65, 70, 75, and 80 mm/h) (Table 3). ROC curve analysis yielded a cut-off value of 55.5 mm/h for preoperative ESR. No cut-off value could be obtained for CRP. At the preoperative ESR cut-off value of 55.5 mm/h, sensitivity was 95.3%, specificity was 87.5%, PPV was 95.3%, and NPV was 87.5%. Sixty-two of 65 patients in the osteomyelitis group (95.3%) and 3 of 24 patients in the control group (12.5%) had ESR above this value.

In correlation analysis, there was no significant relationship between age and ESR ($p>0.05$).

Table 3. Sensitivity, specificity, PPV, and NPV rates at different ESR values

ESR (mm/h)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 60	92.30	91.60	96.70	81.40
≥ 65	89.20	91.60	96.60	75.80
≥ 70	83.00	91.60	96.40	66.60
≥ 75	69.20	91.60	95.70	52.30
≥ 80	50.70	95.80	97.00	41.80

DISCUSSION

Diabetic osteomyelitis is a serious complication that protracts the treatment of diabetic foot infections and increases the rate of amputation (4,5). Although many tests have been developed, their accuracies in the diagnosis of osteomyelitis remain unsatisfactory. Modalities such as MRI, labeled-leukocyte scintigraphy, high-resolution ultrasound, and bone drilling (probe-to-bone test) are used in the diagnosis of osteomyelitis (6,7,8), but bone pathology is still considered the gold standard (9,10,11). Bone biopsy is an invasive procedure, thus compelling clinicians to seek simpler and less invasive diagnostic methods with shorter turnaround times. Inflammatory markers fit these criteria, and there a few studies in the literature investigating their use in osteomyelitis screening and diagnosis (12,13). Although an ESR of 70 mm/h or higher is cited as critical in many guidelines, the number of supporting studies is insufficient. Newman et al. found that all foot ulcer patients with ESR of 70 mm/h or higher had osteomyelitis (14). In a study by Malabu et al., osteomyelitis was detected in 92% of patients with ESR of 70 mm/h or higher, and ESR values within the reference range were significantly more common in patients with no detected osteomyelitis (13). Kalet et al. determined that an ESR of 70 mm/h or higher had a sensitivity of 89.5%, specificity of 100%, PPV of 100%, and NPV of 83%. At lower ESR, sensitivity increased while specificity decreased (15). Ertugrul et al. reported the highest sensitivity at an ESR of

60 mm/h (92%) and highest specificity at 80 mm/h (91%) (1). Mutluoğlu et al. determined an optimal cut-off value of 47 mm/h, which had 72% sensitivity, 84% specificity, and PPV and NPV of 80% and 78%, respectively (16). Michail et al. reported a sensitivity of 61% and specificity of 79% for an ESR of 70 mm/h, while a cut-off value of 67 mm/h had 84% sensitivity, 75% specificity, 71% PPV, and 86% NPV (88). In our study, mean ESR was 86 mm/h in the osteomyelitis group, which was significantly higher than in the control group (43 mm/h).

Evaluations of sensitivity, specificity, PPV, and NPV for different ESRs (17,18,19) revealed a sensitivity of 92.3% for ESR of 60 mm/h and specificity of 95.8% for ESR of 80 mm/h. As ESR increased, sensitivity was reduced while specificity increased. In our study, we determined a sensitivity of 95.3%, specificity of 87.5%, PPV of 95.3%, and NPV of 87.5% for an optimal ESR cut-off value of 55.5 mm/h.

In the present study, ESR had decreased by 42% at postoperative 1 month in the osteomyelitis group and 23% in the control group compared to preoperative values. ESR at postoperative 1 month was above the reference range in the osteomyelitis group (50±21 mm/h) but tended to return to within the reference range in the control group (33±12 mm/h).

For a CRP value of >32 mg/dl, Fleischer et al. reported a sensitivity of 85% and specificity of 65% for osteomyelitis (20). Ertuğrul et al. demonstrated that CRP values were higher in patients with osteomyelitis compared to those with soft tissue infections (1), whereas Mutluoğlu et al. were not able to show a significant difference in CRP between osteomyelitis and soft tissue infections (16). Michail et al. also reported a significant difference in CRP values between osteomyelitis and soft tissue infections. For a CRP value of 14 mg/dl, they determined the sensitivity and specificity to be 85% and 83%, respectively. However, CRP values were within the reference range in about 15% of patients with osteomyelitis and in approximately 60% of patients with soft tissue infection (21). In a study by van Asten et al., CRP was found to be 10.08±8.62 mg/dl in the osteomyelitis group and 5.55±7.88 mg/dl in the group without osteomyelitis (3). In our study, however, CRP level was 95±76 mg/dL (5–283 mg/dL) in the osteomyelitis group and 85±27 mg/dl (40–156 mg/dL) in the control group, with no statistically significant difference between the groups. CRP values in both the osteomyelitis and control groups in our study were high compared to other studies in the literature. This may be attributed to the fact that the patients in our study had serious injuries that required amputation. Because CRP values were not normally distributed, we were not able to calculate sensitivity, specificity, or a cut-off value. CRP values at postoperative 1 month showed a decrease of 77% in the osteomyelitis group and 74% in the control group compared to preoperative values. However, postoperative 1-month CRP had not decreased to within the reference range in the osteomyelitis group (22±27 mg/dl) or the control group (12±5 mg/dl).

CONCLUSION

In summary, when used together with clinical suspicion, ESR is a simple, cost-effective, and rapid diagnostic method with high sensitivity and specificity in the diagnosis of diabetic foot osteomyelitis. However, our results indicate that CRP values respond more rapidly than ESR, suggesting that when evaluating response to treatment, it may be more appropriate to monitor CRP in the short term and ESR in the longer term.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The approval of Cumhuriyet University Ethical Comittee was obtained. Decision date and number 26.07.2017, 2017-07/17.

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