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The Performance of Serum Inflammatory Markers for the Diagnosis and Follow-up of Patients With Osteomyelitis

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Abstract

Serum inflammatory markers, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), and procalcitonin (PCT), have been used for the diagnosis of foot infections in patients with diabetes. However, little is known about their changes during treatment of patients with foot infections. The aim of this prospective study was to examine the performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. A total of 61 patients (age 63.1 ± 7.0 years, 45 men and 16 women, 7 with type 1 and 54 with type 2 diabetes) with untreated foot infection (34 with soft-tissue infection and 27 with osteomyelitis) were recruited. Diagnosis of osteomyelitis was based on clinical examination and was confirmed by imaging studies (X-ray, scintigraphy, magnetic resonance imaging). Determination of the inflammatory markers was performed at baseline, after 1 week, after 3 weeks, and after 3 months of treatment. At baseline, the values of CRP, ESR, WBC, and PCT were significantly higher in patients with osteomyelitis than in those with soft-tissue infections. The sensitivity and specificity for the diagnosis of osteomyelitis of CRP (cutoff value >14 mg/L) were 0.85 and 0.83, of ESR (cutoff value >67 mm/h) 0.84 and 0.75, of WBC (cutoff value >14 × 10^9/L) 0.75 and 0.79, and of PCT (cutoff value >0.30 ng/mL) 0.81 and 0.71, respectively. All values declined after initiation of treatment with antibiotics; the WBC, CRP, and PCT values returned to near-normal levels at day 7, whereas the values of ESR remained high until month 3 only in patients with bone infection. From the inflammatory markers, ESR is recommended to be used for the follow-up of patients with osteomyelitis.

Keywords

serum inflammatory markers, C-reactive protein, white blood cells, erythrocyte sedimentation rate, procalcitonin, osteomyelitis

Diabetes mellitus is the commonest metabolic disease with increasing prevalence worldwide.[1] About 5% of persons with diabetes are facing foot ulcers each year leading to increasing costs[2,3] and high morbidity and mortality.[4] Treatment of foot ulcers accounts for 15% to 25% of total health care resources for diabetes in high-income countries.[5]

Up to 60% of all foot ulcers are complicated by infection at initial presentation to the clinic.[6,7] Chronic and deeper wounds are more likely to be complicated by osteomyelitis as a consequence of contiguous spread of the microorganisms from soft tissues to periosteum.[7] Osteomyelitis is diagnosed in up to 20% of mild to moderate foot infections and in 50% to 60% of severely infected wounds.[8] Osteomyelitis delays wound healing, resulting in recurrence of foot ulcers and its presence increases the likelihood of surgical intervention, amputation, and the duration of treatment with antibiotics.[8,9]

Diagnosis of osteomyelitis in patients with foot ulcers is based on clinical examination and imaging studies.[9] Deep and large ulcers, ulcers with exposed bones, and those that do not heal after appropriate wound care and off-loading are more probable to be complicated by osteomyelitis.[9] The probe to bone test has a positive predictive value of 0.57 and a negative predictive value of 0.98 for diagnosing osteomyelitis in high-risk diabetic subjects.[10,11] Imaging

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Table 1. The Demographic and Clinical Characteristics of the Study Subjects.

	Total	Soft Tissue Infection	Osteomyelitis	*P*
N; n (%)	61 (100)	34 (55.7)	27 (44.3)	
Age in years (mean ± SD)	63.1 ± 7.1	63.79 ± 8.3	62.12 ± 5.02	.33
Male/female; n (%)	45 (73.8)/16 (26.2)	23 (67.6)/11 (32.4)	22 (81.5)/5 (18.5)	.22
Type 1/type 2 diabetes; n (%)	7 (11.5)/54 (88.5)	3 (8.8)/31 (91.2)	4 (14.8)/23 (85.2)	.46
HbA1c in % (mean ± SD)	8.3 ± 1.4	8.2 ± 1.3	8.4 ± 1.5	.84
Hemoglobin in g/dL; mean ± SD	12.3 ± 1.6	12.7 ± 1.5	12.1 ± 1.7	.68
PAD; n (%)	11 (18.3)	5 (14.7)	6 (22.2)	.51
IDSA infection severity; n (%)				
Mild	32 (52.5)	20 (58.9)	—	
Moderate	25 (41.0)	12 (35.3)	25 (92.6)	
Severe	4 (6.5)	2 (5.8)	2 (7.4)	<.001

Abbreviations: PAD, peripheral arterial disease; IDSA, Infectious Diseases Society of America.

studies such as plain X-rays, nuclear scintigraphy, or magnetic resonance imaging (MRI) are currently being suggested for the diagnosis of osteomyelitis[9]; MRI provides the greatest accuracy for the detection of bone infection in the diabetic foot with a sensitivity of 0.90 and specificity of 0.79 to 0.82.[9]

Increased serum inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been used for the diagnosis of bone infection with a sensitivity and specificity of >0.70.[12-16] Procalcitonin (PCT) is a peptide hormone released by non-neuroendocrine parenchymal cells throughout the body, with serum levels typically <0.10 ng/mL in healthy individuals and very high levels (>50 ng/mL) in patients with severe bacterial infections.[17] Determination of serum PCT has been examined in a few studies and it was shown that serum PCT cannot differentiate soft-tissue infections from osteomyelitis.[15-20]

Treatment of patients with osteomyelitis with antibiotics usually lasts several weeks to months together with surgical removal of sequestra.[9] An important issue in the management of patients with osteomyelitis is the monitoring of response to treatment. No guidelines exist for the follow-up of such patients and the management is mainly empirical. In addition, no data exist on the changes of inflammatory markers during treatment to guide clinicians when to discontinue antibiotics. The aims of the present prospective study were, first, to examine the changes of serum inflammatory markers in response to treatment in patients with diabetic foot infections and second, to examine their performance for the diagnosis of confirmed osteomyelitis.

Patients and Methods

A total of 61 consecutive patients with type 1 and type 2 diabetes were recruited from the outpatient foot clinics of 2 hospitals. Inclusion criteria required that the patients had diabetic foot infection and they were not on treatment with antibiotics. Diagnosis of infection was based on the presence of ≥2 classic findings of inflammation (erythema, warmth, tenderness, pain, or induration) or purulent secretions according to the Infectious Diseases Society of America guidelines.[9] Infections were then classified into mild (superficial and limited in size and depth), moderate (deeper or more extensive), or severe (accompanied by systemic signs or metabolic perturbations).[9] The diagnosis of osteomyelitis was based on clinical examination (positive probe-to-bone test) and was confirmed by plain X-rays, nuclear scintigraphy, or MRI.[9] Peripheral arterial disease status was assessed by palpation of pedal pulses or determination of ankle brachial index using a portable Doppler machine; values <0.9 were considered abnormal. Blood was drawn for immediate determination of white blood cells (WBC) and ESR. CRP was measured in serum with the BN ProSpec System (Siemens Healthcare Diagnostic Products GmbH, Marburg, Germany; inter- and intra-assay coefficient of variation <4%) and PCT levels were measured in serum (Liaison Brahms PCT, DiaSorin S.p.A. Saluggia, Italy; inter- and intra-assay coefficient of variation <4%) by 2-site immunoluminometric assay. The study was approved by the ethics committees of the 2 hospitals and informed consent was obtained by all participants. The demographic and clinical characteristics of the participants are shown in Table 1.

Statistical Analysis

Analyses were performed using the SPSS 15.0 statistical package. Differences between the patients with soft-tissue infection and osteomyelitis were tested using parametric or nonparametric methods according to the specific indications, whereas a χ^2 test was used to compare categorical data. The area under the receiver operating characteristic curve of the studied inflammatory markers for the diagnosis

Table 2. The Values of the Inflammatory Markers at Baseline and During Follow-up of the Patients With Diabetic Foot Infections.[a]

	Baseline	7 Days	21 Days	3 Months	P^b	P^c
White blood cells ($\times 10^9$/L)						
Soft tissue infection	14.4 ± 1.7	13.6 ± 1.3	12.6 ± 1.1	11.9 ± 0.7	<.001	
Osteomyelitis	16.2 ± 1.3	14.1 ± 1.2	13.2 ± 0.8	12.1 ± 0.5	<.001	<.001
Erythrocyte sedimentation rate (mm/h)						
Soft tissue infection	65.8 ± 5.1	57.1 ± 4.7	45.0 ± 7.1	35.1 ± 4.3	<.001	
Osteomyelitis	76.1 ± 10.3	70.5 ± 8.6	60.2 ± 8.2	42.9 ± 4.8	<.001	<.001
C-reactive protein (mg/L)						
Soft tissue infection	8.7 ± 2.6	6.8 ± 2.5	5.1 ± 2.5	2.7 ± 1.9	<.001	
Osteomyelitis	25.1 ± 7.6	12.4 ± 3.6	7.1 ± 3.7	3.8 ± 1.6	<.001	<.001
Procalcitonin (ng/mL)						
Soft tissue infection	0.71 ± 0.48	0.48 ± 0.26	0.35 ± 0.20	0.18 ± 0.08	<.001	
Osteomyelitis	2.41 ± 0.10	0.73 ± 0.12	0.60 ± 0.12	0.54 ± 0.10	<.001	.01

[a]Data are shown as mean value ± standard deviation.
[b]*P* values indicate the result of analysis of variance for repeated measurements within each group (*P* value for the effect of time).
[c]*P* values indicate the result of analysis of variance for repeated measurements between the 2 groups (soft tissue infection and osteomyelitis; time × group interaction).

of osteomyelitis was calculated. In addition, analysis of variance for repeated measurements was performed to test the timing effect of the studied parameters in the follow-up of the patients. The same analysis was used to examine for differences during follow-up between patients with soft-tissue infections and osteomyelitis. The Greenhouse–Geisser adjustment was used when the sphericity assumptions were not fulfilled. *P* values <.05 were considered statistically significant.

Results

A total of 34 patients had soft-tissue infection and 27 had osteomyelitis. Patients with soft-tissue infection and osteomyelitis did not differ in terms of gender, age, and type of diabetes, whereas more patients with osteomyelitis had infection of moderate severity in the group of patients with osteomyelitis (Table 1). HbA1c values and peripheral arterial disease status were not different between the 2 groups.

At baseline, 50% of the patients with soft-tissue infection had normal WBC value (<10 × 10^9/L); 6.3% had ESR <30 mm/h and 43.8% had ESR <50 mm/h; 58.8% had CRP <10 mg/L; and 85.3% had PCT <0.5 ng/mL. At baseline, 25.9% of the patients with osteomyelitis had normal WBC value; 7.7% had ESR <30 mm/h and 11.5% had ESR <50 mm/h; 14.8% had CRP <10 mg/L and 14.8% had PCT <0.5 ng/mL. The values of all inflammatory markers at baseline were significantly higher ($P < .001$) in the patients with osteomyelitis than in the patients with soft-tissue infection (Table 2).

During follow-up, all values of the inflammatory markers declined in response to therapy. The values of WBC, CRP, and PCT returned to near-normal levels by day 21 in patients with soft-tissue and bone infection, whereas ESR remained high only in patients with osteomyelitis.

The performance of the inflammatory markers for the diagnosis of osteomyelitis at baseline for various cutoff values is shown in Table 3. All inflammatory markers had adequate sensitivity (>0.70) and specificity (>0.70) to distinguish soft-tissue infection from bone infection in more than 70% of the cases as it is indicated by the receiver operating characteristic analysis. The optimum performance was for WBC > 14 × 10^9/L, ESR >67 mm/h, CRP >14 mg/L, and for PCT >0.30 ng/mL.

Discussion

The main finding of the present study is that all inflammatory markers decline after initiation of treatment with antibiotics in patients with diabetic foot infection and that ESR is probably the best marker to monitor the response to therapy in patients with osteomyelitis. In addition, we found that all inflammatory markers have adequate performance, but lower in comparison with imaging techniques-for the diagnosis of osteomyelitis.

The current guidelines suggest that diagnosis of osteomyelitis should be based on clinical examination and imaging studies.[9] From the clinical criteria, the probe to bone test is highly suggestive of osteomyelitis, but a negative test does not exclude the diagnosis.[9,16] Lavery et al[21] found that the probe to bone test had a positive predictive value of 0.57, but the negative predictive value approached 0.98. Based on these results, the authors concluded that the diagnosis of osteomyelitis should not be made entirely with the probe to bone test and that osteomyelitis can be safely ruled out if the test is negative.[21] Plain films are widely available and relatively inexpensive, and thus make a good initial screening tool for the diabetic foot infection. However, although the specificity for the diagnosis of osteomyelitis is high (0.80), the sensitivity is low (0.54) because the changes

Table 3. The Performance (95% Confidence Intervals) of the Inflammatory Markers at Baseline for the Diagnosis of Osteomyelitis.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Area Under the Curve
WBC ($\times 10^9$/L)					0.78 ± 0.06 ($P < .001$)
10	0.74 (0.57-0.91)	0.50 (0.33-0.67)	0.6 (0.44-0.76)	0.66 (0.47-0.85)	
12	0.74 (0.57-0.91)	0.54 (0.37-0.71)	0.62 (0.46-0.78)	0.68 (0.50-0.86)	
14	0.74 (0.57-0.91)	0.82 (0.69-0.95)	0.65 (0.47-0.83)	0.81 (0.68-0.94)	
15	0.55 (0.36-0.74)	0.85 (0.73-0.97)	0.79 (0.61-0.97)	0.65 (0.50-0.80)	
ESR (mm/h)					0.73 ± 0.07 ($P = .002$)
30	0.92 (0.82-1.00)	0.16 (0.04-0.28)	0.52 (0.39-0.65)	0.67 (0.32-1.00)	
50	0.88 (0.76-1.00)	0.47 (0.30-0.64)	0.62 (0.47-0.77)	0.8 (0.63-0.97)	
67	0.84 (0.70-0.98)	0.75 (0.60-0.90)	0.73 (0.57-0.89)	0.86 (0.74-0.98)	
70	0.61 (0.43-0.79)	0.79 (0.65-0.93)	0.74 (0.56-0.92)	0.67 (0.52-0.82)	
CRP (mg/L)					0.75 ± 0.07 ($P = .001$)
10	0.85 (0.72-0.98)	0.59 (0.42-0.76)	0.67 (0.52-0.82)	0.8 (0.64-0.96)	
11	0.85 (0.72-0.98)	0.71 (0.56-0.86)	0.75 (0.6-0.9)	0.83 (0.69-0.97)	
14	0.85 (0.72-0.98)	0.83 (0.70-0.96)	0.71 (0.54-0.88)	0.77 (0.62-0.92)	
17	0.77 (0.61-0.93)	0.89 (0.78-1.00)	0.88 (0.76-1.00)	0.79 (0.65-0.93)	
PCT (ng/mL)					0.78 ± 0.06 ($P < .001$)
0.3	0.81 (0.66-0.96)	0.71 (0.56-0.86)	0.65 (0.48-0.82)	0.81 (0.67-0.95)	
0.4	0.66 (0.48-0.84)	0.80 (0.67-0.93)	0.77 (0.62-0.92)	0.7 (0.53-0.87)	
0.5	0.55 (0.36-0.74)	0.89 (0.78-1.00)	0.83 (0.67-0.99)	0.66 (0.51-0.81)	
0.6	0.44 (0.25-0.63)	0.95 (0.88-1.00)	0.90 (0.75-1.00)	0.63 (0.49-0.77)	

Abbreviations: WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin.

in bone structure can take up to 2 weeks to manifest.[9,16] Triple phase bone scanning has high sensitivity (0.80) but low specificity (0.20), whereas the leukocyte scan with indium labeling has sensitivity and specificity of 0.88 and 0.86, respectively.[22,23] However, its high cost, the complexity of the white blood cell labeling, the limited availability, and the comparable performance with MRI has eliminated its use for the diagnosis of osteomyelitis. MRI is more sensitive and specific than other imaging modalities and is the method of choice for diagnosing bone infections.[9] A meta-analysis reported the sensitivity of MRI to detect osteomyelitis ranged from 0.77 to 1.00 and specificity from 0.40 to 1.00.[24]

Regarding CRP, Jeandrot et al[19] found higher CRP in increasing grades of diabetic foot infection. Fleischer et al[14] showed that CRP >32 mg/L has a sensitivity of 0.85 and specificity of 0.65 for the diagnosis of osteomyelitis. Ertugrul et al[25] showed that patients with osteomyelitis had higher CRP levels than those with soft-tissue infections. On the contrary, Uzun et al[18] described no differences in CRP between patients with and without diabetic foot infection and Mutluoğlu et al[20] in a small number of patients found no significant differences in serum CRP levels between patients with and without osteomyelitis. In the present study, we found that patients with osteomyelitis had higher serum CRP levels than those with soft-tissue infections and that CRP level of 14 mg/L had a sensitivity of 0.85 and a specificity of 0.83 for the diagnosis of osteomyelitis. CRP values >30 mg/L had low sensitivity (0.23) but high specificity (0.92) for osteomyelitis. However, it should be noticed that almost 60% of the participants with soft-tissue tissue and 15% with bone infection had normal (<10 mg/L) CRP levels.

Previous studies found elevated ESR levels in patients with osteomyelitis.[14,20,25,26] An ESR >70 mm/h had a sensitivity of 0.89 and specificity of 1.00 for osteomyelitis according to Kaleta et al.[26] Ertugrul et al[25] found that a cutoff level of 65 mm/h had a sensitivity of 0.88, a specificity of 0.73, a positive predictive value of 0.78, and a negative predictive value of 0.78 in diabetic patients with osteomyelitis. Another study[20] proposed a cutoff level of 47 mm/h as optimal (sensitivity 0.72, specificity 0.84, positive predictive value 0.80, and negative predictive value 0.78) for the diagnosis of osteomyelitis. In our study, an ESR of 70 mm/h had 0.61 sensitivity and 0.79 specificity, whereas the optimal cutoff level for ESR was 67 mm/h with 0.84 sensitivity, 0.75 specificity, 0.71 positive predictive value, and 0.86 negative predictive value. A small number of patients (<10%) in our study with either soft-tissue or bone infection had low ESR values.

We found that WBC values were significantly higher in patients with osteomyelitis in comparison with those with soft-tissue infection. In addition we showed that a WBC value of 14×10^9/L had a sensitivity of 0.74, a specificity of 0.82, a positive predictive value of 0.65, and a negative predictive value of 0.81 for osteomyelitis. Neither Ertugrul

et al[25] nor Mutluoğlu et al[20] found differences in WBC between patients with or without osteomyelitis. In agreement with previous reports reviewed before,[16] we found that a significant number of patients (50% with soft-tissue infection and 26% with osteomyelitis) had normal WBC.

There are limited data in the literature for PCT in diabetic foot patients. Altay et al[27] found high levels of PCT in diabetic foot infections at baseline, which declined in the first 14 days after treatment initiation with antibiotics. In addition, they did not find differences between patients with deep and superficial infections in terms of PCT, WBC, ESR, and CRP. Uzun et al[18] found increased PCT in patients with diabetic foot infection in comparison with those without infection, but they did not provide data for patients with osteomyelitis. Another small study[20] described no differences between patients with and without osteomyelitis and concluded that PCT cannot distinguish osteomyelitis in diabetic foot infections. We found higher serum PCT concentrations in patients with osteomyelitis in comparison to those having soft-tissue infection. In addition, we showed that the optimum cutoff level for PCT to distinguish osteomyelitis from soft-tissue infection was 0.30 ng/mL, with a sensitivity of 0.81, a specificity of 0.71, a positive predictive value of 0.65, and a negative predictive value of 0.81. Furthermore, 85% of the patients with soft-tissue infection and almost 15% of the patients with osteomyelitis had normal (<0.50 ng/mL) levels.

Interpreting the results of plasma inflammatory markers, we have to take into consideration their kinetics during infections. Circulating neutrophils have a half-life of 6 to 8 hours, start rising in the first hours after infection and return to normal after 2 to 3 days. ESR rises in 1 to 2 days, peaks in 1 week, and takes several weeks to come back to normal; its value is affected by age, gender (slightly higher in females), and hemoglobin. CRP has a half-life of 18 hours, starts rising within 4 to 6 hours, peaks in 48 hours, and returns to normal in 3 to 7 days. PCT has a half-life of 24 hours, starts rising in the first 6 hours after infection, peaks in 24 hours, and returns to normal in 5 to 6 days in response to treatment.

A question for clinicians during management of patients with osteomyelitis is when to discontinue treatment with antibiotics. Although there are no tests that have been proven to correlate with long-term resolution of osteomyelitis, the recent Infectious Diseases Society of America guidelines suggest that a decrease in previously elevated inflammatory markers, especially ESR, resolution of any overlying soft-tissue infection, healing of the wound, and evolution of radiographic changes that suggest healing can be used as criteria for discontinuation of treatment with antibiotics.[9] In the present study, we showed that all inflammatory markers decline early in response to treatment. However, although WBC, CRP, and PCT values return to the near-normal range in the first 3 weeks of treatment in patients with both soft-tissue and bone infection, the values of ESR continue to be high (>45 mm/h) after this time only in patients having osteomyelitis. Thus, our data are the first to show that over a 3-month period, high ESR values imply persistence of bone infection and indicate the need for continuation of treatment with antibiotics.

The strength of our study is that we examined a relatively large number of patients with foot infections and we followed-up them for a period of 3 months. However, there are several limitations. First, we include a small number of patients with severe infections. This may account for the lower values of inflammatory markers, especially for CRP, and certainly including more patients with severe infections could alter the cutoff values. Second, although the observational period is large, we do not provide data for the outcome; larger studies with outcome data of osteomyelitis in relation to inflammatory markers are needed.

The clinical implications of the findings of the present study can be summarized as follows: inflammatory markers such as ESR, CRP, WBC, and PCT may increase in patients with foot infection and higher values are suggestive for the presence of osteomyelitis. Treatment with antibiotics results in decline of CRP, WBC, and PCT in patients with either soft-tissue infection or osteomyelitis and, therefore, they are of limited value for the follow-up of patients with bone infection. However, ESR values decline only in patients with soft-tissue infection but not in patients with osteomyelitis. Therefore, persistently increased ESR levels denote active bone infection and the need for continuation of treatment with antibiotics. Importantly, ESR is an examination of low cost and widely available. We suggest monthly determination of ESR, together with clinical and radiographic criteria, to monitor osteomyelitis activity.

In conclusion, we showed that on average the values of all inflammatory markers are increased in patients with diabetic foot infections and higher values were found in patients with osteomyelitis. However, they cannot be used for the diagnosis of bone infection because they overlap with those obtained by patients with soft-tissue infections. The values of all markers declined after initiation of treatment with antibiotics; the WBC, CRP, and PCT values returned to near-normal levels in the first week of treatment, while the values of ESR remained high for 3 months only in patients with bone infection. Determination of ESR is the best inflammatory marker for the follow-up of patients with osteomyelitis, as persistent abnormal values parallel with infection activity. Therefore, ESR, but not WBC, CRP, or PCT, can be included in the clinical and radiographic armamentarium for the monitoring of patients with osteomyelitis.

Declaration of Conflicting Interests

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