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Clinically Role of Serum Procalcitonin and C-reactive Protein Concentration in Diabetic Foot Ulcer Infections

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Abstract:

Aim: *- 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. Procalcitonin (PCT) has been recently accepted as a marker for diagnosing infection. The aim of the present study was to determine whether PCT levels are associated with infection severity of diabetic foot ulcers and whether PCT levels would be helpful to differentiate infected diabetic foot ulcer (IDFU) from IDFU associated with other infectious diseases (IDFU + O).*

Methods: *- This research was conducted in a Sardar Patel Medical College, Bikaner over the 2016 academic year. We prospectively included 95 diabetic patients hospitalized for IDFU. Infection severity of diabetic foot ulcers was graded according to the Infectious Diseases Society of America-International Working Group on the Diabetic Foot clinical classification of diabetic foot infection. Chest radiograph, urinalysis, urine microscopy, urine culture, and blood cultures (if fever was present) were performed for all patients to diagnose other infectious diseases. Laboratory parameters were measured from blood venous samples. Quantitative data from mid-year examination marks were analysed at the end of the academic year.*

Results: *- PCT (0.286, $P < 0.001$) and C-reactive protein (0.368, $P < 0.001$) levels were significantly associated with infection severity of diabetic foot ulcers. However, only PCT levels could differentiate patients with associated infectious diseases from patients with no concomitant infection (area under the receiver-operator characteristic curve 0.729, $P < 0.0001$; cut-off value 0.44; sensitivity 88.7; specificity 70.2).*

Conclusion: *-PCT and CRP levels positively correlated with infection severity of diabetic foot ulcers and PCT levels > 0.48 ng/mL in patients with IDFU may be associated with other systemic bacterial infection.*

Keywords: ***Diabetic foot Ulcer, Infections, Procalcitonin, C-reactive protein.***

1. Introduction

Approximately 15-25% of diabetic patients have foot ulcers during their lifetime.[1] Diabetic foot ulcers are frequently infected.[2] Fifty-nine percent of diabetic foot amputations have been attributed to infection and infected diabetic foot ulcer (IDFU) is a major causal factor for lower-limb amputation.[3,4] Conventional laboratory markers, such as erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and C-reactive protein (CRP), cannot differentiate between infectious and non-infectious inflammation and are of limited value in the diagnosis of diabetic foot infection.[5-

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[7] Serum Procalcitonin (PCT) level is elevated in patients with systemic bacterial infections and, unlike other markers, it is usually not elevated in patients with inflammation due to viral infection or non-infectious diseases. Thus, serum PCT has higher diagnostic accuracy for the diagnosis of bacterial infection than standard biochemical parameters, such as the WBC count and serum CRP levels.[8-10] Hence, there has been an interest in investigating the usefulness of PCT for the diagnosis of diabetic foot infection. It has been reported in the literature that PCT levels have higher efficiency in distinguishing IDFU from a non-infected diabetic foot ulcer, followed by CRP, WBC, and ESR levels, and that the combination of PCT and CRP measurements increase the accuracy of predicting diabetic foot infection.[11-13] We postulated that PCT would be useful to assess the infection severity in diabetic foot ulcers and other infectious diseases. Because diabetic foot infection is progressive and associated with the potential risk of gangrene and limb amputation, diabetic foot infection has a high morbidity and mortality rate.[11,14-16] Therefore, prompt and adequate diagnosis and treatment of diabetic foot infection is critical to reduce the amputation and mortality rate. The aim of the present study was to determine whether PCT levels are associated with infection severity of diabetic foot ulcers and whether PCT levels are helpful in differentiating IDFU from IDFU + O.

2. Materials and methods

2.1. Patients

This study was approved by the S.P.Medical college, Institutional Research Board. Between june 2016 to july 2016, we prospectively included consecutive diabetic patients hospitalized for infected diabetic foot ulcer. The same foot and ankle surgeon in our department examined all patients in order to grade infection severity, according to the Infectious Diseases Society of America-International Working Group on the Diabetic Foot (IDSA-IWGDF) clinical classification of diabetic foot infection[17] and IDFU was diagnosed if the grade of infection was ≥ 2. Chest radiograph, urinalysis, urine microscopy, urine culture, and blood cultures (if fever was present) were performed on every patient to diagnose other infectious diseases, such as sepsis, pneumonia, and urinary tract infection. Where an abnormal laboratory test result was obtained or other infectious diseases were clinically suspected, the patient was referred to the department of infectious diseases, in order to confirm the diagnosis of concomitant infectious diseases. Inclusion criteria were as follows: infection grade ≥ 2 according to the IDSA-IWGDF criteria, no history of antimicrobial treatment within the previous 6 months, and no history of surgery in the previous 6 weeks. The exclusion criteria were malignancy, inflammatory disease, and immunosuppressive treatment.

2.2. Laboratory parameters

A venous blood sample was obtained from all patients on admission, before the commencement of antimicrobial treatment, to measure the following: WBC and neutrophil count, ESR, CRP, and PCT. For analyzing the PCT levels, blood samples were collected in serum separating tubes and centrifuged for 20 min at 3500 rpm, after being maintained at room temperature for 20 min. PCT levels were measured using an electrochemiluminescent immunoassay analyzer (Roche Diagnostics, Meylan, France), and the functional detection limit was 0.02 ng/mL. The Department of biochemistry, Clinical laboratory analyzed the PCT while WBC and differential blood counts, CRP, and ESR were analysed in pathology department..

2.3. Statistical analysis:

Statistical analyses were performed using the software package SPSS for Windows version 16.0.0 (SPSS Inc., Chicago, Illinois). The Mann–Whitney U test or Kruskal-Wallis test were used to compare the continuous variables. To assess the correlation between the grade of infection severity and laboratory parameters, Spearman rho correlation coefficients were calculated for patients with no associated infectious diseases, to avoid the effect of other causes of infection. Comparisons of the correlation coefficients were performed with the Ztest, using the Fisher's Z transformation. A receiver operating characteristic (ROC) analysis and the area under the ROC curve (AUC) were calculated to measure the accuracy of the laboratory parameter to distinguish patients with IDFU from patients with IDFU + O. The best cut-off value was calculated, and specificity and sensitivity of the laboratory parameters were determined using the best cut-off value. Comparison of the ROC curves was performed to compare the accuracies of laboratory markers for distinguishing the grades of infection severity. A P value < 0.05 was considered statistically significant.

Tables 1:- Demographics

Age (mean ± SD years)	62.6 ± 7.9
Sex (n,%)	
Male	81 (85.26 %)
Female	14 (14.73 %)
Duration of DM[a] (mean ± SD years)	16.8 ± 5.2
Infection Severity grade[b] (n,%)	

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2	24 (25.26 %)
3	59 (62.10 %)
4	12 (12.63 %)
Combined other infections (n,%)	
No	83 (87.36%)
Yes	12 (12.63 %)
Pneumonia	7 (7.36 %)
Urinary tract infection	3 (3.15 %)
Sepsis[c]	2 (2.10 %)

a. DM- Diabetes mellitus.
b. IDSA-IWGDF Clinical Classification of Diabetic Foot Infection.
c. One patient had Pneumonia, One patient had Urinary tract infection,One patient had Pneumonia.

Table 2: Laboratory Parameters according to the infection grade in IDFU without any other infectious disease

Parameters	Grade 2 (n=20)	Grade 2 (n=59)	Grade 2 (n=05)	P value
ESR (mm/h)	60.75±30.30	68.25±29.40	72.15±30.43	0.598
CRP (mg/L)	32.20±32.28	58.10±53.28	141.48±48.62	<0.001
PCT (ng/ml)	0.15±0.22	0.18±0.23	3.44±3.32	<0.001
WBC ($\times10^9$/L)	8.62±1.80	8.89±3.12	10.34±3.02	0.221
Neutrophils($\times10^9$/L)	6.64±2.10	5.84±2.94	7.68±3.10	0.102

Table 3: Laboratory parameters in IDFU[a] and IDFU[b]+O

Parameters	IDFU (n=83)	IDFU+O (n=12)	P value
ESR (mm/h)	68.65±30.74	76.26±15.64	0.156
CRP (mg/L)	60.21±57.23	78.62±73.65	0.456
PCT (ng/ml)	0.58±1.58	1.02±1.22	<0.001
WBC ($\times10^9$/L)	8.62±3.20	9.10±3.63	0.419
Neutrophils($\times10^9$/L)	6.32±2.45	7.84±3.84	0.213

[a] *IDFU ,infected diabetic foot ulcer.*
[b] *IDFU+O, infected diabetic foot ulcer associated with other infectious disease.*

3. Results

A total of 95 patients diagnosed with infected diabetic foot ulcer (grade _ 2, IDSA-IWGDF criteria) were included in this study (mean age 62.6 years; range, 40–88 years, ±7.4 years). The distribution of infection according to severity, using IDSA-IWGDF criteria, was as follows: grade 2 (24 patients, 25.26%), grade 3 (59 patients, 62.10%), and grade 4 (12 patients, 12.63%). Twelve patients (12.63%) had other infectious diseases in addition to IDFU. Of these, 7 (7.36%) patients had pneumonia, 3 (3.15%) patients had a urinary tract infection, and 2 (2.10%) patients had sepsis (Table 1). Among the 2 patients diagnosed with sepsis, one had pneumonia, one had urinary tract infection, and one had pneumonia and urinary tract infection. In patients without any other infectious diseases, the comparison of laboratory parameters among the grades of infection severity of diabetic foot ulcers is shown in Table 2. There were significant differences in the PCT and CRP levels among the infection grades ($P < 0.001$ for both). The correlation analysis in patients with no other infectious diseases demonstrated that PCT (Spearman's q 0.338, $P < 0.001$) and CRP (Spearman's q 0.477, $P < 0.001$) positively correlated with the grade of infection severity of diabetic foot ulcers.

4. Discussion

The most important findings of the present study was that PCT and CRP levels were significantly associated with an increased IDFU infection grade and that PCT was a useful diagnostic marker to differentiate patients with IDFU from patients with IDFU + O. Procalcitonin, the 166 amino acid precursor of calcitonin, is produced by the thyroid C cells.[18] Serum PCT concentration is generally very low in healthy patients, but PCT production is activated in all parenchymal tissues and concentrations increase rapidly following bacterial infection.[19,20] Production of PCT is stimulated directly by bacterial endotoxins and lipopolysaccharides and indirectly by inflammatory mediators, such as tumor necrosis factor-alpha, interleukin-6, and interleukin-1.[21] However, mediators of viral infection, such as interferon-gamma, attenuate PCT levels.[22] Therefore, PCT has recently been recognized as a more specific marker of bacterial infection.[13] A number of

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studies have been conducted to investigate the diagnostic accuracy of PCT in differentiating between infected and non-infected diabetic foot ulcers, but the results have not been consistent.[11-13,23] Two out of 4 studies showed that PCT was the most useful marker among conventional laboratory markers[11,13], while 1 study reported that CRP showed the greatest sensitivity and specificity to distinguish IDFU from non-infected diabetic foot ulcers.[12] A further study reported that ESR was the most sensitive and specific inflammatory marker.[23] Three of these studies concluded that the combination of PCT and CRP or ESR was the most sensitive method to distinguish infected from non-infected diabetic foot ulcers.[12,13,23] Studies have also evaluated the diagnostic value of PCT to distinguish osteomyelitis from soft tissue infection in patients with diabetic foot infection.[24,25] One study reported that PCT failed to identify patients with bone infection[25], while another study suggested that PCT is useful to distinguish osteomyelitis in infected foot ulcers.[24] Reports indicate that PCT and CRP levels correlate with the severity of infection. In children with liver disease, PCT and CRP correlated with infection severity.[26] A linear relationship between PCT and CRP values and the severity of infection has been previously demonstrated by Hatherhill et al. in a study involving 175 children admitted to the paediatric intensive care unit.[27] A number of studies have demonstrated that higher PCT levels were present in patients with IDFU than in patients with non-infected diabetic foot ulcer; however, the correlation between PCT levels and infection severity of diabetic foot ulcers was not analyzed.[11,13,23] Our study assessed the correlation between laboratory parameters and infection severity of diabetic foot ulcers, and showed that PCT and CRP levels positively correlated with infection severity. However, ROC analysis demonstrated that CRP was a use-intensive care unit of patients with diabetic foot ulcers.[29] Therefore, it is important to be aware of major cardiac events and nosocomial infection when treating patients with IDFU. The present study sought to determine whether PCT is useful to differentiate IDFU from IDFU + O and, to the best of our knowledge, this has not been examined previously. CRP values have been shown to significantly increase in response to local infection, while local infection, without systemic manifestations, only results in a limited increase in PCT levels.[28] PCT levels are generally higher in patients with severe and systemic infection.[30] A prospective study evaluating the predictive value of PCT levels to identify systemic infection showed that, in multivariate analysis, the only variable associated with systemic infection was the Procalcitonin level, while body temperature, WBC count, and CRP, were not associated with systemic bacterial infection.[31] Furthermore, in the present study, only PCT was found to have a diagnostic value to distinguish patients with IDFU from those with IDFU + O, such as systemic bacterial infection, including pneumonia; urinary tract infection; and sepsis. There are some limitations to this study. First, we performed a chest radiograph, urinalysis, urine microscopy, urine cultures, and blood cultures (in the presence of fever) on admission to diagnose sepsis, pneumonia, and urinary tract infection. Therefore, infectious diseases on admission, other than those indicated above, may not have been diagnosed. However, during hospitalization no patients were diagnosed with infections other than sepsis, pneumonia, and urinary tract infection. Second, the grade of infection severity of diabetic foot ulcers was determined on the basis of clinical examination only, according to the IDSA-IWGDF clinical classification. Therefore, there may have been inter observer variability in grading infection severity. Finally, the reliability of PCT levels remains controversial as these are subject to changes, according to age, pathogen, and type of infection.[23] Different types of pathogens cause different types of immune response and therefore, result in a variable degree of increase in PCT [18]. It has been noted that PCT levels are greatly elevated in patients with infections associated with Gram-negative bacteria, compared to Gram-positive bacteria.[32] Non-infectious conditions, such as stress response (i.e., after surgery, trauma, shock, burns), Kawasaki disease, and adult onset Still's disease also can cause elevated PCT levels.[18,33-35] Even though PCT may incur extra costs in addition to the costs of conventional laboratory markers in patients with IDFU, it has been demonstrated to be cost-effective in a hospital setting to guide antibiotic usage in septic patients, when decreased length of stay and quality-of-life-years are considered.[36-38] However, there are only a limited number of theoretical studies investigating the impact of PCT on the costs incurred by patients with systemic bacterial infections. Therefore, further studies are needed to evaluate the cost effectiveness of PCT in patients with IDFU.

5. Conclusion

Although PCT and CRP levels positively correlated with the grade of infection severity of diabetic foot ulcers, only CRP was useful as a laboratory parameter for distinguishing diabetic foot infection grades 2 and 3. PCT levels were elevated (>0.59 ng/mL) where infected diabetic foot ulcer was associated with other systemic bacterial infection. Therefore, infected diabetic foot ulcers should be managed promptly and we should consider the presence of other infectious diseases, in addition to diabetic foot infection, when PCT levels are elevated.

Conflict of interest

All authors declare the have no conflict of interest.

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