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RESEARCH ARTICLE

Procalcitonin as a Biomarker for Diabetic Foot Ulcer

Hamid Owaysee Osquee[a], Abolfazl Pourhassan[a], Parisa Sadeghian[a], Hadi Pourjafar[b] and Fereshteh Ansari[c,*]

[a]*Department of Infectious Diseases, Tabriz University of Medical Sciences, Tabriz, Iran;* [b]*Department of Public Health, Maragheh University of Medical Sciences, Maragheh, Iran;* [c]*Research Center for Evidence-Based Medicine, Health Management and Safety Promotion Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE HISTORY

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Abstract: ***Background*:** Diabetic foot ulcer is a common disorder involving diabetic patients. Appling new indicators of the severity of diabetic foot infection may help the practitioners to develop more efficient diagnosis and treatment strategies.

***Methods*:** In this study, 70 diabetic patients with a foot ulcer, admitted to the infectious diseases ward of Tabriz education and treatment center between 2015 and 2016, were enrolled. The severity of infection was determined according to the Infectious Diseases Society of America clinical practice guideline. Twenty of these patients were excluded and further examinations were performed on 50 patients. On the first day of hospitalization and before antibiotic therapy, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), Procalcitonin (PCT), White blood cells (WBCs), Fasting blood sugar (FBS) and HbA1C were measured. The level of these factors was then compared across four severity groups.

***Results*:** Pulse rate, respiratory rate, body temperature and leukocyte count were significantly higher in the patients with severe infection. ESR and CRP were higher in patients with more severe infection, but PCT and HbA1C level were not in accordance with the infection's severity.

***Conclusion*:** In conclusion, ESR and CRP level can be more successfully used to discriminate patients, according to the severity of the infection.

Keywords: Diabetic foot ulcer, biomarker, procalcitonin, infection, CRP, HbA1C.

1. INTRODUCTION

Diabetes is a global health concern with a prevalence of 5-11% in different countries. It has been estimated that about 380 million adults are living with this problem [1]. Diabetic foot ulcer (DFU) is one of the major complications of diabetes which affects 10%-25% of patients. DFU is associated with lower extremity amputation and increased risk of mortality [2].

The correct classification of patients may help the practitioners to identify the ones at a higher risk of imputation and other complications and may help them to administer antibiotics in a safe and correct way. Many classification schemes have been applied for categorizing patients with a diabetic foot ulcer based on the severity of the infection (Table **1**). One of the most recent and valid systems was developed by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) in 2004 [3].

Several laboratory markers have also been used for defining the severity and predicting the ampu-

*Address correspondence to this author at the Iranian evidence-based center of excellence, Tabriz University of Medical Sciences, Iran; Tel/Fax: +984133342219, +984133342219;
E-mail: fereshtehansari66@gmail.com

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tation risk in patients with a diabetic foot ulcer. Leukocytosis, anemia, high fasting blood sugar (FBS), elongation of erythrocyte sedimentation rate (ESR), high level of C reactive protein (CRP) and reduction of Hb are some of these parameters [4, 5] (Table **2**).

Traditional laboratory factors are not able to differentiate non-infected from infected inflammation, therefore we need more specific biomarkers to assess the severity of a diabetic foot ulcer. Procalcitonin (PCT) has been introduced as a potential biomarker for this purpose. PCT is the prehormone of calcitonin and its production is modulated by lipopolysaccharides and sepsis-related cytokines. From the early 20th century, several studies have been performed to evaluate PCT as a marker of bacterial infection [6]. The first studies on this subject revealed different results, however, the net result suggests that PCT accuracy was higher than CRP to detect bacterial infection [6].

The accuracy of this marker in the diagnosis of foot infection and in predicting amputation surgery in patients with DFU has been previously studied [7-10], although there is a debate about the applicability of PCT for DFU diagnosis in practice.

In this study, we assessed the association of PCT level with the severity of DFU and studied its capability for discrimination of DFUs in patients with different levels of infection according to the IDSA-IWGDF criteria [11].

2. MATERIALS AND METHODS

This study was approved by the Tabriz University of medical sciences Review Board. A written consent form was obtained from each patient and an attempt was made to keep the personal information of patients confidential.

All the diabetic patients with foot ulcer who were admitted to the infectious diseases ward of Tabriz education and treatment center between 2015 and 2016, were enrolled in this case series. For each patient, the grade of infection severity was determined according to the Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections [12]. Patients with concomitant infectious diseases, including sepsis, urinary infection, pneumonia, meningitis were excluded from the study. Malignancy, inflammatory diseases such as inflammatory Bowel disease (IBD) and rheumatoid arthritis and taking immunosuppressive drugs or antibiotics before inclusion in the study, were other exclusion criteria. On the first day of hospitalization and before antibiotic therapy, a venous blood sample was obtained from all patients to measure the following parameters: ESR, CRP, PCT, WBC, Fasting blood sugar (FBS) and Glycoside hemoglobin (HbA1C).

To determine the PCT level, the samples maintained at room temperature for 30 minutes and then centrifuged for 20 minutes (BRAHMS PCT kit Roche-Germany) with a functional detection limit of 0.05ng/mL were applied to determine the serum level of PCT. Biochemistry laboratory of the hospital analyzed ESR, CRP, WBC, FBS and HbA1C.

The distributions of background variables and the level of laboratory levels in four severity groups were examined. For gender (qualitative variable), chi-square test was used. For other variables, Kolmogrov-Smirnov test was used to test the normality of data distribution. ANOVA or Kruskal-Wallis statistical tests were then performed to compare each parameter across four severity groups. All the statistical analyses was carried out using SPSS ver. 21.

3. RESULTS

Seventy patients with a diabetic foot ulcer were enrolled in this study. We excluded 20 of them according to the exclusion criteria: antibiotic consumption during the last 4 months (4 patients), acute leukocytosis (1 patients), rheumatoid arthritis (2 patients), psoriasis (1 patients), undergoing surgery within the last 6 weeks (2 patients), concomitant infection in other organs (6 patients), gout (1 patients), Necrotizing Fascitis (3 patients).

Finally, 50 patients were included (28 (56%) male and 22 (44%) female). The mean±SD of the age of participants was 58.96±11.13 with the minimum of 34 and the maximum of 82 years. The mean time of the onset of diabetic ulcer was 21.54 days (SD=30). According to the IDSA-IWGDF criteria, the distribution of ulcer severity was as followed: Foot ulcer without infection =13 (26%), mild=6 (12%), moderate=17 (34%) and severe=14 (28%). Twenty three (26%) of patients were diagnosed with amputation surgery [13].

Table 1. Baseline and clinical characteristics of patients with a diabetic foot ulcer stratified by severity of the injury.

Characteristics	Foot Ulcer Without Infection (n=13)	Mild (n=6)	Moderate (n=17)	Severe (n=14)	P Value*
Gender (n of males (%))	5 (38.5) [a]	4 (66.7) [a]	13 (76.5) [a]	6 (42.9) [a]	0.123
Age (mean±SD)	58.46±10.61 [a]	51.00±10.28 [a]	62.65±11.69 [a]	58.36±10.34 [a]	0.172
Pulse rate (mean±SD)	81.54±6.79 [a]	81.67±3.88 [a]	82.00±7.86 [a]	98.36±15.55 [b]	0.001
Respiratory rate (mean±SD)	16.62±1.66 [a]	15.83±1.33 [a]	17.00±1.66 [a]	21.29±5.54 [b]	0.001
Body temperature (mean±SD)	36.91±0.46 [a]	36.95±0.34 [a]	37.16±0.51 [a]	38.26±0.36 [b]	<0.001

* P value of one way ANOVA test for age, Kruskal-Wallis test for pulse rate, respiratory rate, and body temperature, and chi square test for gender.
Different letters indicate significant differences between groups in each row.

Table 2. Distribution of laboratory parameters in patients with diabetic foot ulcer stratified by severity of the injury (n=50).

Laboratory Parameters	Foot Ulcer Without Infection (n=13)	Mild (n=6)	Moderate (n=17)	Severe (n=14)	P Value*
WBC ($\times 10^9$/L) (mean±SD)	9.32±2.81 [a]	10.30±2.80 [a]	9.72±3.15 [a]	15.64±3.93 [b]	<0.001
ESR (mm/h) (mean±SD)	32.31±27.47 [a]	37.67±17.98 [a]	58.00±33.26 [ab]	84.79±29.28 [b]	<0.001
CRP (mg/L) (mean±SD)	20.72±28.37 [a]	32.17±33.39 [a]	55.47±37.04 [ab]	91.00±13.47 [b]	<0.001
PCT (ng/ml) (mean±SD)	0.10±0.13 [a]	0.49±0.74 [ab]	0.44±0.90 [ab]	1.42±3.81 [b]	0.025
HbA1C (%)	10.91±1.84 [a]	9.90±1.69 [ab]	8.62±1.84 [b]	9.85±1.65 [ab]	0.010

* P value of one way ANOVA test for WBC, ESR and H1A1C, and Kruskal-Wallis test for CRP and PCT.
Different letters indicate significant differences between groups in each row.

4. DISCUSSION

We aimed to identify the most compatible biomarkers with IDSA-IWGDF criteria which have been introduced as a useful method to differentiate the patients according to the severity of the disease. In this study, we assessed several clinical and laboratory features in four groups of patients; DFU with no infection, DFU with a mild infection, DFU with moderate infection and DFU with severe infection.

Clinical features and a leukocyte count of patients with severe infection were generally different from patients with no infection or lower severity of diabetic foot infection. Pulse rate, respiratory rate, body temperature and leukocyte count were significantly higher in these patients, but these parameters were not different among patients in lower severity groups (*i.e.*, no infection, mild and moderate infection).

ESR was higher in patients with higher grades of infection. As shown in other studies ESR is a good discriminant tool to define the stage of infection of the deeper layers of skin [14, 15]. However, in our study at stage 3 of infection, ESR was not significantly higher than no infection and moderate infection stages. In stage 3, the infection invaded subcutaneous tissues and we expected to see a significantly higher level of ESR. This may be due to low sample size.

CRP showed an ascending trend and its level was higher in patients of higher severity classifications in comparison with lower severity. However,

the statistical analysis revealed that CRP is not able to differentiate patients with no infection and patients with mild and moderate infection. The difference between patients with moderate and severe infection was also not significant. In a similar study, it has been demonstrated that CRP can be successfully used to differentiate infected and non-infected DFU [8].

The PCT was not significantly different in patients with no infection, and patients with mild and moderate infection. PCT level was almost similar in patients in each of the three levels of infection. This marker could just separate patients with no infection and patients with severe infection.

HbA1C was not very different in patients with and without infection and patients of different severity groups. The level of this factor was extremely higher than the standard level [16] in all the severity groups, and it may be the cause of diabetic foot ulcer.

The results show, unless the potential beneficial effects of PCT to diagnose the bacterial infection, it is not suggested as a biomarker for a diabetic foot ulcer. However the sample size of the study was limited, and future studies may reach, more precise results with a larger sample size. According to the results of this study, ESR and CRP are more useful, and we recommend other researchers to try to identify new and more applicable biomarkers to evaluate the severity of diabetic foot ulcer.

CONCLUSION

The results of this study suggest that ESR and CRP are more compatible with the infection's severity, determined according to the Infectious Diseases Society of America clinical practice guideline. These two factors can be used as helpful biomarkers to establish diagnosis and treatment plans for DFU.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Tabriz University of medical sciences Review Board.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008.

CONSENT FOR PUBLICATION

A written consent form was obtained from each patient and an attempt was made to keep the personal information of patients confidential.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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