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ORIGINAL ARTICLE

The role of procalcitonin as a marker of diabetic foot ulcer infection

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Abstract

Foot ulcers are frequent in diabetic patients and are responsible for 85% of amputations, especially in the presence of infection. The diagnosis of diabetic foot ulcer infection is essentially based on clinical evaluation, but laboratory parameters such as erythrocyte sedimentation rate (ESR), white blood count (WBC), C-reactive protein (CRP) and, more recently, procalcitonin (PCT) could aid the diagnosis, especially when clinical signs are misleading. Fifteen diabetic patients with infected foot ulcers were admitted to our department and were compared with an additional group of patients with non-infected diabetic foot ulcers (NIDFUs). Blood samples were collected from all patients in order to evaluate laboratory markers. In the current study, the diagnostic accuracy of PCT serum levels was evaluated in comparison with other inflammatory markers such as CRP, ESR and WBC as an indicator to make the distinction between infected diabetic foot ulcers (IDFUs) and NIDFUs. CRP, WBC, ESR and especially PCT measurements represent effective biomarkers in the diagnosis of foot infections in diabetic patients particularly when clinical signs are misleading.

Introduction

Foot ulcers are common in diabetic patients, with 15–25% estimated to experience such an ulcer during their lifetime (1). Foot ulcers are responsible for 85% of amputations in diabetic patients (2–6) and have a high morbidity and mortality rate (7), so early diagnosis and adequate treatment are essential to prevent amputation.

Diabetic foot ulcers are often infected and lead to amputation more often than non-infected ulcers.

In 2004, the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) published a system for grading infection severity (8,9), underlining that diagnosis of infection must be based not on microbiological findings but on clinical criteria. Failure to follow these recommendations results in

Key Messages

- infection is one of the most frequent complications of diabetic foot ulcers
- the diagnosis of infected diabetic foot ulcers (IDFUs) is mainly based on clinical findings
- in our study we compared a group of patients with IDFUs with a group of patients with non-infected diabetic foot ulcers (NIDFUs)
- we evaluated several blood biomarkers in both groups such as erythrocyte sedimentation rate (ESR), white blood count (WBC), C-reactive protein (CRP) and procalcitonin (PCT)

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- PCT levels had higher efficiency in distinguishing diabetic foot ulcer infection from non-infected ulcers, followed by CRP levels, WBC and ESR

unnecessary antimicrobial treatment that leads to the emergence of multidrug-resistant bacterial strains, increasing costs and possibly causing drug-related adverse events (8).

Biochemical parameters such as erythrocyte sedimentation rate (ESR), leucocytosis and circulating inflammatory proteins are known to be of poor value for diagnosing diabetic foot infections as, even in the most severe cases, there are few systemic manifestations (10,11). Procalcitonin (PCT), a 116-amino acid protein precursor of the hormone calcitonin, has recently gained acceptance as a marker for diagnosing infection (12–15). Some authors claim that its accuracy as a predictor of bacterial infection is higher than that of C-reactive protein (CRP) (12). PCT remains fairly low in viral infections and non-specific inflammatory diseases (16).

In this study, the diagnostic accuracy of PCT was evaluated in comparison with other inflammatory markers such as CRP, ESR and white blood cell count (WBC) as an indicator to make the distinction between infected diabetic foot ulcers (IDFUs) and non-infected diabetic foot ulcers (NIDFUs).

Materials and methods

Between June and August 2015, 15 diabetic patients affected by infected foot ulcers and admitted to the unit of vascular surgery, Bianchi-Melacrino-Morelli Hospital of Reggio Calabria, Italy were enrolled in the current study. An additional group of patients with clinical NIDFU was also included in the study.

Exclusion criteria included other infectious diseases such as sepsis, meningitis, pneumonia, inflammatory bowel disease, surgery in the previous 3 weeks, haematological disease and all the diseases known to raise the value of PCT. Also, patients who received immunosuppressive therapy or antibiotic therapy in the previous 3 weeks were excluded.

IDFU diagnosis was based on the IDSA guidelines, and it was identified in presence of purulent secretion or a combination of two of the following signs: warmth, tenderness, pain, induration, redness.

At admission, all patients were subjected to blood samples withdrawn before the eventual initiation of antimicrobial treatment for the measurements of WBC, ESR, CRP and PCT. The blood taken for the analysis of PCT levels was centrifuged for 20 minutes after being maintained at room temperature for 30 minutes, with a functional detection limit of 0·06 ng/ml. Levels of CRP, WBC and ESR were assessed by the hospital biochemistry laboratory.

Deep tissue sampling from foot ulcers was submitted for microbiological examination to identify the germ involved in the infection. Wound localisation (toe, metatarsal, middle foot, heel, leg) and purulent secretion were noted. With respect to age and gender, there was no statistically significant difference between the two groups ($P > 0{\cdot}05$).

Table 1 Demographics and comorbidities of IFDU and NIDFU groups

	IDFU N (%)	NIDFU N (%)
Sex		
Male	11 (73·3)	10 (66·7)
Female	4 (26·7)	5 (33·3)
Mean age (years)	65·6	63·4
Comorbidities		
Diabetes mellitus	15 (100)	15 (100)
Hypertension	12 (80)	10 (66·7)
Myocardial ischaemia	6 (40)	7 (46·7)
Renal failure	4 (26·7)	5 (33·3)
Active smokers	5 (33·3)	4 (26·7)
Dyslipidaemia	5 (33)	6 (40)
Atrial fibrillation	2 (13·3)	3 (20)
Chronic obstructive pulmonary disease	6 (40)	5 (33·3)
HCV	1 (6·7)	—

HCV, Hepatitis C Virus; IDFU, infected diabetic foot ulcer; NIDFU, non-infected diabetic foot ulcer.

Results

Demographic characteristics and comorbidities of patients of both groups are summarised in Table 1, while wound localizations and characteristics are reported in Table 2. The group of patients with IDFU included 11 males (73·3%) and 4 females (26·7%), with a mean age 65·6 years, all affected by diabetes mellitus and on insulin treatment, presenting the following risk factors and comorbidities: hypertension (12, 80%), myocardial ischaemia (6, 40%), renal failure (4, 26·7%), active smoking (5, 33·3%), dyslipidaemia (5, 33·3%), atrial fibrillation (2, 13·3%), chronic obstructive pulmonary disease (6, 40%), and HCV (1, 6·7%). Eleven patients (73·3%) with a deep ulcer with purulent secretion, three patients (20%) with a deep ulcer in absence of purulent secretion and one patient (6·7%) with a superficial ulcer were presented to our institution. We recorded two metatarsal ulcers (13·3%), four heel ulcers (26·7%), three mid foot ulcers (20%), two mid foot and leg ulcers (13·3%) and one mid foot and toe ulcer (6·7%) while the localisation was only on the toes in three patients (20%). Eleven patients (73·3%) had fever > 38·5°C at admission. Microbiological cultures of tissue samples revealed an infection caused by *Staphylococcus aureus* in eight patients (53·3%), *Pseudomonas aeruginosa* in three cases (20%), *Enterococcus faecalis* in two patients (13·3%), *Streptococcus agalactiae* in one patient (6·7%) and a polimicrobic infection in one patient (6·7%).

All patients were started on specific antibiotic therapy as per the microbiological results.

The group of patients with NIDFU included 10 males (66·7) and 5 females (33·3), with a mean age 63·4 years, all affected by diabetes mellitus, with the following risk factors: hypertension (10, 66·7%), myocardial ischaemia (7, 46·7%), renal failure (5, 33·3%), active smoking (4 ,26·7%), dyslipidaemia (6, 40%), atrial fibrillation (3, 20%) and chronic obstructive pulmonary disease (5, 33·3%). The ulcers presented the following localisations and characteristics: toe (4, 26·7%), metatarsal (2, 13·3%), mid foot (4, 26·7%), mid foot and toe (3, 20%), heel (2, 13·3%). Three patients (20%) had superficial ulcers while 12 (80%) presented deep ulcers.

Table 2 Wound localisation and characteristics of IDFU and NIDFU groups

Wound localisation	IDFU N (%)	NIDFU N (%)
Toe	3 (20)	4 (26·7)
Metatarsal	2 (13·3)	2 (13·3)
Mid foot	3 (20)	4 (26·7)
Mid foot and leg	2 (13·3)	—
Mid foot and toe	1 (6·7)	3 (20)
Heel	4 (26·7)	2 (13·3)
Wound characteristics		
Superficial ulcer	1 (6·7)	3 (20)
Deep ulcer	3 (20)	12 (80)
Deep ulcer and purulent secretion	11 (73·3)	—

IDFU, infected diabetic foot ulcer; NIDFU, non-infected diabetic foot ulcer.

Table 3 Infection markers in IDFU and NIDFU groups

Groups	ESR (mm/hour)	CRP (mg/dl)	WBC (10^9/l)	PCT (ng/ml)
IDFU group ($n = 15$)	53·27	121·32	15·980	2·92
NIDFU group (n=15)	48	11·08	11·346	0·028
	$P = 0·4661$	$P = 0·00009$	$P = 0·0095$	$P < 0·00001$

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IDFU, infected diabetic foot ulcers; NIDFU, non-infected diabetic foot ulcers; PCT, procalcitonin; WBC, white blood cell count.
Data inserted are mean values. P is considered significant for values $< 0·05$.

Laboratory parameters of both groups are listed in Table 3 as mean values. The PCT and CRP levels in IDFU group were significantly higher than those in the NIDFU ($P < 0·00001$ and $P = 0·00009$ respectively). ESR levels ($P = 0·4661$) and WBC levels ($P = 0·0095$) were higher in the IDFU group than in the other group, with a minor statistical significance with respect to PCT and CRP.

Discussion

Foot infection is one of the most frequent complications of diabetes mellitus, with a difficult and long healing process. The diagnosis of IDFU is essentially based on clinical findings, but the evaluation of inflammatory markers such as CRP, WBC, ESR and more recently PCT could favour the diagnosis of infection when clinical signs are misleading.

PCT has been shown to be superior to other infection markers in the diagnosis of both systemic and localized bacterial infections, but only a few studies are present in literature about its value in IDFU. Serum PCT levels are variable and depend on the site and extension of the infection. Considering for PCT a cut-off value of 0·06 ng/ml, in the IDFU group, we observed values that ranged from 0·66 and 7·82, with higher values in cases of extended infection, while in the NIDFU group we observed values < 0·06, with a significant statistical difference ($P < 0·00001$).

CRP, an acute-phase protein, increases during inflammatory processes and is higher in diabetic patients than in healthy subjects (17). Upchurch *et al.* (18) demonstrated that CRP levels were higher in the IDFU group than in NIDFU group as also confirmed in our study in which CRP levels were significantly higher in the IDFU group than in the other group ($P = 0·00009$).

WBC is a universal accepted marker of infection as confirmed in our study, in which WBC levels were significantly higher in the group of patients with IDFU than in NIDFU group ($P = 0·0095$).

In the current study, the parameter with minor statistical significance in order to distinguish IDFU from NIDFU was ESR ($P = 0·4661$).

Only a few studies have surveyed the role of PCT in distinguishing IDFU from NIDFU (19–21). Uzun *et al.* (19) showed in their study that ESR, WBC and PCT are essential in the diagnosis of IDFU, while CRP did not have an important role, a finding inconsistent with the results of the current study. In addition, they demonstrated that PCT has the highest area under the curve and the greatest statistical significance in relation with infection, as in our study.

Jeandrot *et al.* (20) reported that CRP was the most useful marker, having the highest sensitivity and specificity to distinguish IDFU from NIDFU. The higher performance of CRP, compared with PCT, may be explained by the mild nature of infection in grade 2 diabetic foot ulcers: CRP values have been shown to significantly increase in response to local infection, while local infection without systemic manifestations results only in a limited increase in PCT levels (22).

They also showed that WBC and neutrophil counts were of little value in diagnosing a mild infection in DFU as there was no significant difference between grade 2 and grade 1 ulcer patients or the control group: this poor informative potential of haematological parameters confirms the findings of previous studies (10,11).

The main finding of the prospective study proposed by Jeandrot *et al.* (20) was that combining the measurements of CRP and PCT increased the accuracy of predicting wound infection.

The higher efficiency of ESR in denoting infection, compared with PCT, could be rationalised by the mild nature of infection in low-grade diabetic foot wounds.

Jafari *et al.* (21) in their study showed that ESR was the most sensitive and specific inflammatory marker distinguishing IDFU from NIDFU. For these authors, CRP was less significant than ESR and more than PCT or WBC. The higher efficiency of ESR in denoting infection, compared with PCT, could be rationalised by the mild nature of infection in low-grade diabetic foot wounds. They also demonstrated that a higher level of PCT is present in higher grades of IDFU; PCT levels are usually higher in patients with severe and systemic infection (23). Like Uzun *et al.* (19) and Jeandrot *et al.* (20), Jafari *et al.* (21) also concluded that the highest sensitivity was obtained when the two markers (such as CRP and PCT or ESR and PCT) were considered together in order to distinguish IDFU from NIDFU.

Conclusion

In conclusion, in our study that included 15 diabetic patients with clinical signs of infection and 15 diabetic patients without

clinical signs of infection, PCT levels had higher efficiency in distinguishing IDFU from NIDFU followed by CRP, WBC and ESR levels.

A correct and prompt diagnosis of IDFU is essential to prevent systemic infections and lower limb amputations, reducing the morbidity and mortality rate. To obtain a correct diagnosis of IDFU, we propose the association of clinical signs with the evaluation of laboratory parameters such as ESR, CRP, WBC and PCT. The highest sensitivity is probably obtained when at least two markers (such as CRP and PCT, or ESR and PCT) are considered together in order to distinguish IDFU from NIDFU.

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