Procalcitonin to diagnose and monitor biopsy proven diabetic foot osteomyelitis
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Abstract

Objective: Diabetic foot osteomyelitis (DFO) requires early diagnosis and aggressive treatment. In this prospective study we examined the value of procalcitonin (PCT) and other conventional serum markers, to diagnose and monitor osteomyelitis in the diabetic foot.

Research design and Methods: We included 36 patients that were admitted to our tertiary hospital with an infected diabetic foot ulcer (IDSA moderate/severe). Patients were divided in two groups based on results of culture and/or histopathology of bone biopsy specimens. PCT, white blood cells (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured at baseline, after 3 weeks and 6 weeks of standard therapy.

Results: PCT was the most informative marker to differentiate between osteomyelitis and soft tissue infection at baseline ($p=0.0486$). CRP, ESR and PCT levels significantly declined in the group with osteomyelitis after starting therapy. When comparing with the non-osteomyelitis group CRP and ESR decreased significantly during follow-up ($p=0.0209$ and $p=0.0173$ respectively).

Conclusions: Our results suggest that PCT might be of value for distinguishing osteomyelitis and non-osteomyelitis infected foot ulcers. The serum markers CRP and ESR can give you direction when monitoring these patients but should not be used to diagnose osteomyelitis.

As part of the worldwide epidemic of diabetes mellitus, the prevalence of lower extremity complications is rising and patients with diabetes are now confronted with a 12-25% lifetime risk of developing a foot ulcer.[1,2] The occurrence of foot ulcers bodes poorly for clinical outcomes and is reported to be an independent risk factor for lower extremity amputation and mortality.[3,4] Ulcers often become infected and early diagnosis of soft tissue infection is essential to prevent the spread of infection into bone. Up to 66% of the persons admitted to the hospital with a diabetic foot infection have osteomyelitis.[5] Patients with osteomyelitis undergo more surgeries and have longer treatment duration with intravenous antibiotic compared to patients with an isolated soft tissue infection.[6]

Because the clinical spectrum of diabetic foot infections is wide, it is difficult to predict the extent and severity of the infected ulcer.[7] Additionally, the local immune response to an infection may not be evident in patients with diabetes.[8,9,10] Though optimal antibiotic management of the infected ulcer is important, limited access of inflammatory cells may make it hard for antimicrobials to penetrate the infected tissue.[11] Diagnostic tools to diagnose osteomyelitis include the probe to bone test, with a high negative predictive value in high-risk patients[12] and magnetic resonance imaging (MRI), with a reported sensitivity of 0.90 and specificity of 0.79 to 0.82.[13] However, the histologic and microbiologic examination of osteomyelitis using bone biopsy remains superior, with a reported diagnostic sensitivity of 0.95 and specificity of 0.99.[14] Further to confirmation of the diagnosis, bone specimens can be used for culture to identify the bacterial pathogen and direct antibiotic therapy, reducing the risks of suboptimal therapy and resistance. [15]

Procalcitonin (PCT) is a 116-amino acid peptide hormone released by parenchymal cells throughout the body, with serum levels typically <0.05ng/ml in a healthy individual. A large body of evidence supports the use of serum PCT as a helpful tool in distinguishing bacterial from viral and non-specific inflammatory diseases.[16,17] A systemic review of Shen et al[18] reported a high positive likelihood ratio (LR+: 6.48; 95%CI: 2.88-14.6) of PCT for the identification of bone and joint infection in patients who present with fever and orthopedic symptoms. Only few small studies have evaluated the value of PCT to distinguish diabetic foot infections.[19,20 21, 22]

An important issue in the treatment of patients with osteomyelitis is monitoring success of therapy. The duration of optimal treatment varies widely in the literature and the efficacy of various antibiotic classes remains unknown.[23, 24] Results of imaging are affected by the prolonged bone marrow edema after surgical treatment, trauma and/or Charcot and can lag behind clinical signs and symptoms.[25,26] A recent study by Altay et al.[20] evaluated the value of inflammatory markers to monitor response to therapy in patients with DFO. PCT, C-reactive protein and Interleukin-6 levels were significantly decreased in patients without foot osteomyelitis after 14 days of therapy but stayed elevated in patients with osteomyelitis. In another study by Michail et al.[19] the erythrocyte sedimentation rate remained high after 3 months of therapy in patients with DFO.

In this study, we aimed to assess the value of PCT in clinical practice to distinguish osteomyelitis from soft tissue infection and to determine the role of this serum marker in monitoring therapy.

Research Design and Methods

Study design

We conducted a prospective cohort study comparing biomarkers in patients with diabetic foot osteomyelitis admitted to our tertiary care hospital with patients admitted with soft tissue infection of the foot. Patients were followed up for 6 weeks and received standard of care, including surgical treatment if needed. We included patients who were 21 years or older and had a moderate or severe infected ulcer based on the Infectious Diseases Society of America (IDSA) classification.[11] Exclusion criteria were other infectious diseases, a history of active bone infection, immunosuppressive therapy, organ and/or hematological malignancies and end stage renal disease requiring dialysis. During the baseline visit we collected patient characteristics and preformed an extensive neurological and vascular examination. We evaluated the peripheral arterial disease status by determination of the ankle brachial index using a portable Doppler machine: values <0.9 were considered abnormal. Segmental skin perfusion pressure and pulse volume recordings were measured using a Sensilase Pad-IQ system.[27] Peripheral neurologic status of both feet was assessed using monofilament sensory and vibration threshold perception tests. The diagnosis of osteomyelitis was confirmed by positive histopathological examination and/or culture of bone at the clear surgical margin or from a percutaneous bone biopsy.

Biological parameters

Blood was drawn at baseline, after 3 weeks and 6 weeks for determination of white blood cells (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. CRP, WBC and ESR were analyzed by the hospital biochemistry laboratory. The blood taken for PCT analysis was centrifuged after 30min of collection for 12 minutes at 3000 rpm. 0.1 ml of venous plasma was stored at -80°C for later analysis as a batch to minimize variance. The PCT concentration in serum was measured with an automatic kryptor device using a BRAHMS procalcitonin kit (BRAHMS Diagnostica, Berlin, Germany). The functional sensitivity is reported to be 0.04ng/ml with an intra assay variation lower than 5%.[28] Laboratory technicians were kept unaware of the clinical data.

Statistical analysis

Analysis was performed using the SAS 9.4 statistical package. Differences between the two groups were tested using parametric or non-parametric methods according to the specific indications. Differences between the laboratory levels of the two groups at baseline were measured using the Wilcoxon rank sum test in median. Data were presented as mean +/- standard deviation. 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 and without DFO. The Greenhouse–Geisser adjustment was used when the sphericity assumptions were not fulfilled. *P* values <0.05 were considered statistically significant.

Results

Table 1 presents an overview of the patient characteristics. 36 patients were enrolled at baseline, 1 patient left the hospital against medical advice before we could perform the bone biopsy. 24 patients had a positive bone biopsy for osteomyelitis (DFO group), 11 patients had no evidence of osteomyelitis in their biopsy (NDFO group). There were no females in the negative group (p=0.03). 18 patients (75%) in the positive group had a previous ulcer before they developed the ulcer with osteomyelitis (p=0.007). The PCT levels in the DFO group were significantly higher at baseline than in the NDFO group (p=0.0486).

Table 1 Characteristics of patients from each group

	DFO group *n*=24 (%)	NDFO group *n*=11 (%)	P-value
Sex, male (%)	16 (67)	11 (100)	0.03
Age, years, mean ±SD	50.6 ± 11.7	51.1 ± 8.1	0.11
BMI, mean ± SD; >30 (%)	30.3 ± 5.0 (50)	28.4 ± 5.7 (36.4)	0.70
Tobacco			
Previous Use	13 (54)	6 (54.5)	0.93
Current Use	3 (12.5)	2 (18)	0.66
Diabetes mellitus type 2	21 (87.5)	10 (91)	0.77
ABI, mean ±SD; ABI<0.9 (%)	1.02 ± 0.23 (30.4)	1.01 ± 0.19 (20)	0.71
SPP, mean ±SD			
Great toe (mmHg)	58.3±36.9	78.73±36.3	0.158
Plantar medial forefoot (mmHg)	69.3±25.1	79.45±21.9	0.258
Plantar lateral forefoot (mmHg)	76.3±26.6	77.18±32.2	0.932
Dorsal foot (mmHg)	73.1±39.5	72.3±22.1	0.947
VPT 1st MTPJ, (Hz), mean ± SD	58.51±26.5	41.94±17.0	0.084
Previous DFU	18 (75)	3 (27)	0.007
Temp at baseline, (°C), mean ±SD	36.4 ± 0.8	36.6 ± 0.5	0.24
Depth index wound, mean ± SD (mm)	13.0± 11.6	7.7± 5.7	0.29
Positive PTBT	14 (58)	5 (45)	0.48
White blood cell count, (10^9/L), mean ± SD	8.23 ± 3.62	7.55 ± 3.12	0.58
C-reactive Protein, (mg/dl), mean ± SD	10.08 ± 8.62	5.44 ± 7.88	0.0537
Erythrocyte sedimentation rate, (mm/h), mean ± SD	78.33 ±35.93	58.9 ± 40.25	0.20
Procalcitonin, (ng/ml), mean ± SD	0.26±0.45	0.07±0.07	0.0486
HbA1c, (mmol/mol), mean ± SD	9.76±2.65	10.68±0.45	0.30
Antibiotics at admission	8 (33)	1 (9)	0.22
Antibiotics duration (weeks), mean ± SD	6.29± 2.5	3.45± 2.1	0.48

All data were collected during admission at the baseline visit. DFO, diabetic foot osteomyelitis; NDFO, no diabetic foot osteomyelitis. Fem, female; Mal, male; Bx, bone biopsy; SD, standard deviation; BMI body mass index, defined as weight in kilogram/(length in centimeter)^2; ABI, ankle brachial index; SPP, skin perfusion pressure; VPT, vibration perception threshold; MTPJ, metatarsophalangeal joint; DFU, diabetic foot ulcer; Temp, temperature; PTBT, probe to bone test; AB, antibiotic

Laboratory markers of both groups at all three time points are shown in Figure 1. A significant decrease can be seen in CRP (p=0.0002), ESR (p<0.0001) and PCT (p=0.0483) between baseline and follow-up of the DFO group (Table 2). Compared to the NDFO group only CRP and ESR significantly decreased, p=0.0209 and p=0.0173 respectively.

Figure 1 shows the overview of the 4 markers during follow up.

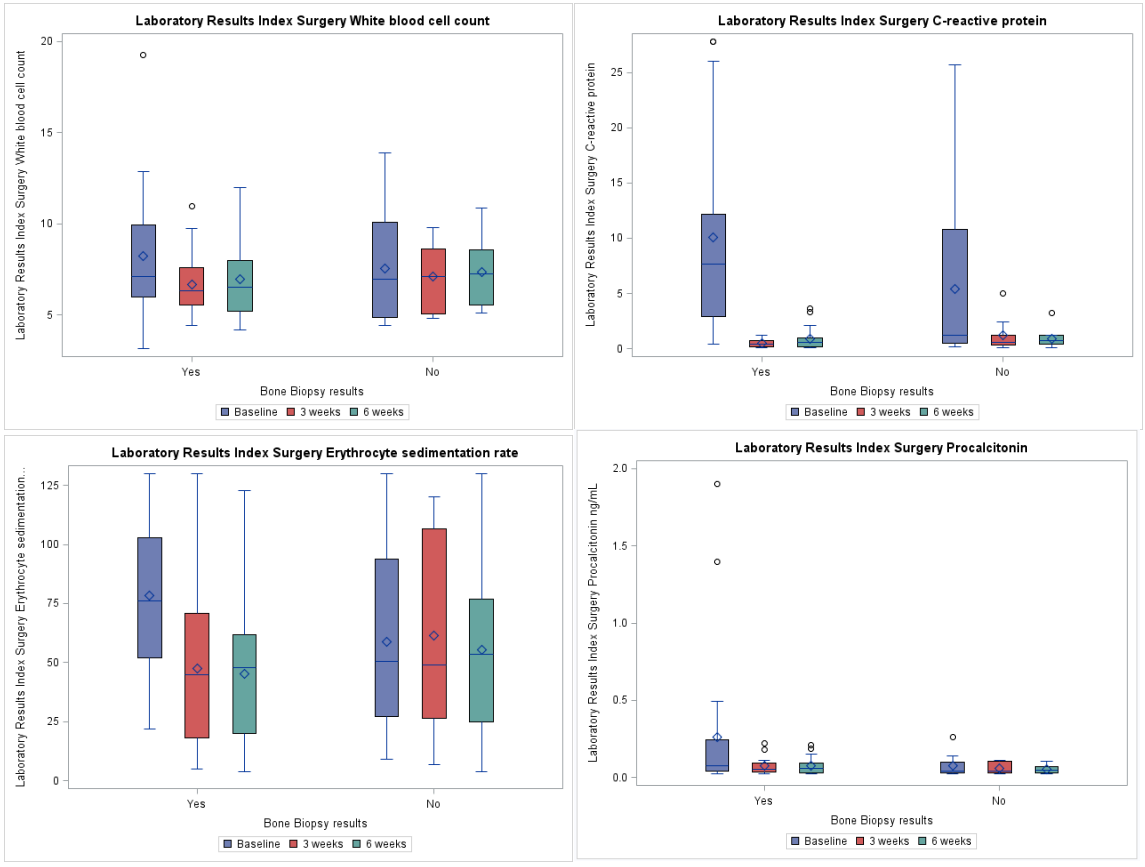

Table 2. Inflammatory Markers at Baseline and During Follow-up

	Baseline *n*=35	3 weeks *n*=30	6 weeks *n*=32	p^b	p^c
WBC (10^9/L)					
Positive Biopsy, mean ± SD	8.23 ± 3.62	6.65 ± 1.63	6.95 ± 2.15	0.1531	
Negative Biopsy, mean ± SD	7.55 ± 3.12	7.12 ± 1.83	7.34 ± 2.01	0.6285	0.55
CRP (mg/dl)					
Positive Biopsy, mean ± SD	10.08 ± 8.62	0.46 ± 0.34	0.9 ± 1.02	0.0002	
Negative Biopsy, mean ± SD	5.44 ± 7.88	1.23 ± 1.58	0.92 ± 0.94	0.096	0.0209
ESR (mm/h)					
Positive Biopsy, mean ± SD	78.33 ±35.93	47.48 ±33.18	45.23 ±28.83	<.0001	
Negative Biopsy, mean ± SD	58.9 ± 40.25	61.38 ±44.31	55.5 ± 40.83	0.3752	0.0173
PCT (ng/ml)					
Positive Biopsy, mean ± SD	0.26±0.45	0.06±0.06	0.06±0.06	0.0483	
Negative Biopsy, mean ± SD	0.07±0.07	0.06±0.04	0.05±0.03	0.2924	0.1785

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 (biopsy results; time ×group interaction).
WBC, white blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin

Conclusions

The results of this study suggest that PCT has an additional value in distinguishing DFO from NDFO (p=0.0486) when patients are admitted to the hospital with an infected diabetic foot ulcer. The performance of CRP to diagnose osteomyelitis was comparable in this study population, with a p-value of 0.0537. In an earlier reported pilot study by Mutluoglu et al.[29] PCT did not reach statistical significance (p=0.627) when comparing 13 DFO patients with 11 patients without bone infection. However, two important differences with the present study might be the reason for this conflicting result. Firstly, Mutluoglu and colleagues used MRI to diagnose DFO, secondly an ELISA kit was used to analyze the serum PCT levels. The higher number of patients in our DFO group (*n*=24) may also have contributed to the difference.

Other studies that looked at PCT in diabetic foot infections underline the diagnostic accuracy of this marker. Uzun et al.[17] studied the usefulness of serum inflammatory markers, including PCT, in detecting bacterial infection in diabetic patients with foot ulcers. The area under the receiver operating characteristic curve for infection identification was greatest for PCT (0.859; p<0.001). Another pilot study of Jeandrot et al.[18] reported the diagnostic value of the combination of PCT with C-reactive protein (AUC 0.947) in diabetic foot ulcer classification. Unfortunately, both studies based their

diagnosis of diabetic foot infection on clinical examination and patients with osteomyelitis were not analyzed as a subgroup. When calculating the AUC of PCT for our patient population, we found a lower area of 0.68 because of overlapping PCT values between groups.

In a case control study by Fleischer et al. [30] a significant difference was found in CRP ($p=0.006$), ESR ($p=0.008$) and WBC ($p=0.043$) at baseline between 34 DFO patients and 20 patients with cellulitis. However, mildly infected ulcers (IDSA classification) were included in the study and osteomyelitis was based on pathology results of "acute osteomyelitis". Ertugrul and colleagues prospectively evaluated 24 DFO patients and found a significant difference in ESR ($p<0.001$) and CRP ($p=0.001$) when comparing them with patients without bone infection.[31] In this study 43% of the patients had a more superficial ulcer (Wagner 0-2)[32] compared to our patient population. Rabjohn et al.[33] had similar preoperative levels of ESR in their osteomyelitis group (76.2 ±35.7 mm/h) and in their control group (59.2±24.7 mm/h) as our study population and found a significant p-value of 0.0221 between groups. However, comparison with this population is difficult because patients without diabetes were included in the analyses.

Most studies evaluating serum inflammatory markers for DFO looked at different cut-off points and incorporated definite cut-off levels in regression models when analyzing prognostic values.[24, 27, 28, 29, 31, 34, 35] However, when looking closer at the results of these studies, mean levels and ranges differ considerably across studies (depending on the study design) and no consensus is reached in a definite cut-off level for any of the mentioned serum markers. By changing continuous variables into bivariate variables, the power of the analysis is affected. Also, one can question how the clinician will use these suggested cut-off points in clinical practice.

While 3 of the 4 tested markers (CRP, ESR, PCT) significantly decreased in the DFO group during therapy they did not significantly decrease in the NDFO group. When we compare these results to a similar designed study of Michail et al.[24], the differentiating value of the serum markers during follow-up seems to be better in our study population. The inflammatory markers in our DFO group seem to be reacting more at standard therapy than the markers in the NDFO group. However, confounding factors like the responsible pathogen, surgical interventions, type of antibiotic therapy, therapy adherence and other events that might have influenced the levels of the markers have to be taken into consideration.

A limitation of our study design is the high pre-test probability of osteomyelitis in the included subjects and following from that the relatively small number of negative subjects. The next step with these data is to define if the bone infection in our included subjects was still there after 6 weeks of therapy and to compare that remission with the inflammatory markers. [36]

To ensure minimal loss of quality of life for patients with diabetic foot ulcers, surgical interventions, long-term treatment with antibiotics and sequential readmissions need to be prevented. Early diagnosis and aggressive treatment of bone infections is therefore

essential when treating these patients. Despite many years of research, no single sufficient criterion has been developed to diagnose osteomyelitis in this population and the answer to this dilemma might be in the combination of a range of different diagnostic tools. Although there is enough evidence that laboratory findings can be of aid in diagnosing and monitoring diabetic foot osteomyelitis, it should be used as an integrated modality in clinical practice rather than as a differentiating finding. Higher values of inflammatory markers are suggestive of DFO but because of big ranges and low reported sensitivity these should not be used to differentiate DFO from soft tissue infections. A decline in levels of serum markers can be used to monitor success of therapy but future trials that determine resolution of bone infection have to proof this assumption.

Acknowledgments

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02/13/2015

Dear Dr. McIndoe,

Enclosed please find our progress report in the form of a submitted manuscript. The purpose of the proposal was to evaluate the value of procalcitonin in diagnosing and monitoring diabetic foot osteomyelitis (3U24 DK076169-08S4, National Institutes of Health). To this end we enrolled 36 patients with diabetic foot infection and diagnosed osteomyelitis with a bone biopsy in 24 of them. We collected serum of all patients at various time points and determined the level of procalcitonin using a BRAHMS procalcitonin kit (BRAHMS Diagnostica, Berlin, Germany). In the manuscript the results of these data are summarized in Table 2 and Figure 1. Procalcitonin was the only inflammatory marker that could differentiate bone infection from soft tissue infection in the enrolled patients. During follow up two other inflammatory markers seem to be valuable. These results raise the strong possibility that inflammatory markers can be used in clinical practice to determine success of therapy in diabetic foot osteomyelitis.

In addition to Procalcitonin , we used department research money to test serum levels of Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNFα), Monocyte Chemotactic Protein-1 (MCP-1) and Macrophage Inflammatory Protein-1 alpha (MIP1α) in the enrolled patients. This study will provide us with further information about the levels of inflammatory biomarkers and their response to therapy. Our results in these two important biomarker studies will lay the groundwork in understanding inflammatory biomarkers in patients with diabetic foot osteomyelitis that will allow for developing rapid, accessible testing as they become more widely available.

Lawrence A. Lavery