The Role of Procalcitonin to Determine Infection in Diabetic Foot Ulcer: An Evidence-Based Case Report

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Abstract

Introduction: Early diagnosis infection in diabetic foot patients remains challenging. Several biomarkers have been used as a diagnostic tool, including procalcitonin. However, the performance of this examination is still questioning.

Aim: This evidence-based case report aims to assess the performance of procalcitonin level to distinguish between infected and non-infected diabetic foot.

Method: Literature searching was performed in Medline, Cochrane, EBSCO, Scopus, and also hand searching. Only articles with cuts off outcome were included.

Result: Patients with diabetic ulcer infection has a higher procalcitonin level compare with those who did not have a disease. Several cuts off provide to diagnose infection in the diabetic ulcer. Uzun et al. found 0.08 and 0.1 as a cut off which performed good specificity and sensitivity.

Conclusion: Procalcitonin helps us to distinguish non-infected and infected diabetic ulcers. The best cut-off value was 0.5 with the 54 % sensitivity and 100 % specificity.

Keywords: *diabetic foot, infection, procalcitonin*

Introduction

Diabetic foot has become a significant problem worldwide. The incidence estimates between 15-25%, 1% of which has undergone a lower limb amputation.[1] The financial burden of diabetic foot ulcers and associated amputations is enormous, approximately £650 million in

England in 2011, exceeding 0.6% of the total health budget.[2] Infection contributed to about 60% of diabetic foot ulcer. The soft tissue infection may spread into the bone resulting in diabetic foot osteomyelitis and thus a high risk of amputation.[1] Thus, early detection and prompt treatment are needed to lower the morbidity and mortality.

One of the early treatment in infected diabetic foot ulcers is to give initial empirical antibiotics. Conversely, unnecessary over-prescription of antibiotics exposes the person to the risk of adverse effects, increases the risk of subsequent infections with resistant organisms and contributes to increasing antimicrobial resistance in society.[2]

Diagnosis of diabetic foot ulcer infection continues to rely on symptoms, principally pain, and signs, including erythema, warmth, edema, and discharge. However, pain may be absent due to concomitant neuropathy, and signs may be attenuated by vasculopathy.[2] Moreover, there may even be no erythema, warmth, pain or tenderness in diabetic foot infection.[3,4] Failure to treat mild infection with antibiotics would risk progression to severe infection and amputation.[2]

Several inflammatory markers such as white blood counts, C-reactive protein, and erythrocyte sedimentation rate (ESR) have been widely used in the uncertain diagnosis of diabetic foot infections.[4] However, several limitations have been known. First, they are not specific.[1] Furthermore, up to 50% of patients with deep tissue infections will not have leukocytosis.[3]

Procalcitonin (PCT), a precursor of calcitonin, is a 116 amino-acid peptide, member of the calcitonin superfamily of peptides. PCT serum level is very low in healthy patients (< 0.1 ng/ml) and rises rapidly in response to bacterial endotoxins.[1] In diabetic foot ulcer, procalcitonin has not routinely used. PCT has been used as a sepsis biomarker in several infections including osteomyelitis in patients with diabetes mellitus.[1] In these reports, we evaluated the use of procalcitonin as a diagnostic aid to distinguish infected and non-infected diabetic foot ulcer.

Clinical Scenario

A-39-year-old woman was admitted to hospital due to worsening the ulcer in her right heel. The abscess arose one month ago in bullae form and changed into a callus. However, in the last week, the sore was getting worse and broader, and also painful; thus she came to the ER. In IDSA-IWGDF (Infectious Disease Society of America – International Working Group on the Diabetic Foot) classification the ulcer was classified as a severe infection. There was no bone involvement from X-ray examinations. There was no prior history of trauma. This patient

had been diagnosed with diabetes for six years ago, the three classic sign of diabetes (polyphagia, polydipsia, polyuria) were present. Weight loss was also observed at about 5 kg in three months. She routinely visits her doctor and the last diabetes medication she received were basal insulin and metformin 500 mg three times daily. She was also diagnosed with stage 4 chronic kidney disease and diabetic retinopathy. She had undergone an eye laser procedure due to hemorrhage in the left retina.

The laboratory findings of this patient were WBC 28,080 hemoglobin 8 and random blood glucose 292. Debridement procedure was done and culture was taken from the infected ulcer. From the microbiological culture, we found *Staphylococcus epidermidis (MRSE)*. This patient was treated initially with ampicillin-sulbactam 1.5 gram 4 times a day as the empirical antibiotic of choice. This antibiotic was used despite microbiological reported resistant due to the decreasing infection in patients.

This patient was already being admitted two weeks before this current admission due to shortness of breath. She was diagnosed as acute lung edema. In the previous admission, the heel ulcer already presents without any sign of inflammation and classified as no infection based on IDSA-IWDF criteria. Thus, the patient did not receive any antibiotics or debridement procedure. The WBCs during the admission was also within normal limits. We wondered whether procalcitonin examination is necessary to perform in this previous admission to start antibiotics earlier before the full-blown infections arouse two weeks later.

Clinical Question

Thus, we formulated the following clinical question: In patients with diabetic ulcer, does procalcitonin can distinguish infected and non-infected diabetic foot ulcer?

- Patients : Patients with diabetic ulcer
- Intervention : Classification based on procalcitonin level (cut off value)
- Comparison : Classification based on IDSA-IWGF criteria
- Outcome : diagnosis of infected diabetic foot ulcer

Methods

Literature searching and reviewing were done in May 2024 in these databases: Medline, Cochrane, EBSCO, and Scopus. Additional searching was also done by looking for the relevant articles in google scholar, garuda.ristekdikti.go.id, and articles cited from the bibliography of selected articles. The keywords for literature searching was based on PICO and their synonyms.

These articles were screened by titles and abstracts using inclusion and exclusion criteria. The inclusion criteria were a cross-sectional study, case-control, or meta-analysis of a cross-sectional study; otherwise, the exclusion criteria were the review, non-humans trial, animal study, etc. Then, we defined the selected articles which assessed the full-text availability dan removed the duplication articles. The final number of useful articles were appraised critically. We assessed validity, importance, and applicability of eligible articles according to Oxford Critical Appraisal Tool 2005. All agreements were made by consensus of two or more reviewers.

Result

We conducted literature searching in several databases. **Table 1** presents the strategy of comprehensive literature searching. The total number of articles from the search were 156 articles. After screening the title and abstract as well as selecting the articles according to inclusion and exclusion criteria, we obtained 19 articles after removing duplication. After reading the full texts, only four articles were appropriate and useful to answer our clinical question. (**Figure 1**). Two reports were excluded due to the unavailable full version. Others were excluded because they did not provide cuts off the value of procalcitonin. All of the articles are a case-control study.

Critical appraisal was done using recommended working sheet for diagnostic research by Oxford CEBM Critical Appraisal Tools. **Table 2** described the essential result of appraisal comprehensively. All the studies using clinical criteria IDSA-IWGDF as a gold standard and all participants also underwent procalcitonin measurement. This measurement categorized as a "hard" or objective measurement, thus the result of this examination is independent. The highest value of post-test probability was achieved by Umapathy, et al.[5] which found 0.5 as a cutoff point. Uzun, et al.[3] also reached the same value of post test probability with 0.08 and 0.1 as a cut off value.

All reports used IDSA-IWGDF clinical criteria to define infection in the diabetic ulcer. Several examinations such as bone probe test and X-ray were used to diagnose osteomyelitis and bone involved infection. However, Umapathy, et al.[5] was the only study using the microbiological report as a confirmation test for diabetic foot infected. Patients with a positive result in microbiological examinations and fulfill the clinical criteria were recruited in that study.

Exclusion criteria were mentioned clearly by all studies, except in study conducted by Jeandrot, et al.[6] Concomitant infections and prior antibiotic treatments which may elevate the

procalcitonin level were excluded by all the studies. Patients with hematological disorders were excluded in several studies.[3–5] Furthermore, only study conducted by Umapathy, et. al.[5] which excluded patients with other types of diabetes. The description of this evidence was depicted in **Table 2**.

Table 1. Strategy for Literature Searching

Database	Keywords (Accessed May 21st 2024)	Number of articles
Medline	((((((diabetic foot[MeSH Terms]) OR diabetic foot[Title/Abstract]) OR diabetic ulcer[MeSH Terms]) OR diabetic ulcer[Title/Abstract])) AND ((infect*[MeSH Terms]) OR infect*[Title/Abstract])) AND ((procalcitonin[MeSH Terms]) OR procalcitonin[Title/Abstract])	49
Cochrane Library	[Title, Abstract, Keywords] (diabetic foot OR diabetic ulcer) AND [Title, Abstract, Keywords] (infection OR infected) AND [Title, Abstract, Keywords] (procalcitonin)	8
Scopus	[TITLE-ABS-KEY] (diabetic foot OR diabetic ulcer) AND [TITLE-ABS-KEY] (infection OR infected) AND [TITLE-ABS-KEY] (procalcitonin)	27
EBSCO	[ABSTRACT] (diabetic foot OR diabetic ulcer) AND [ABSTRACT] (infection OR infected) AND [ABSTRACT] (procalcitonin)	19
Additional Searching	(diabetic foot OR diabetic ulcer OR kaki diabetik OR ulkus diabetik) AND (infected OR infection OR terinfeksi) AND (procalcitonin)	85

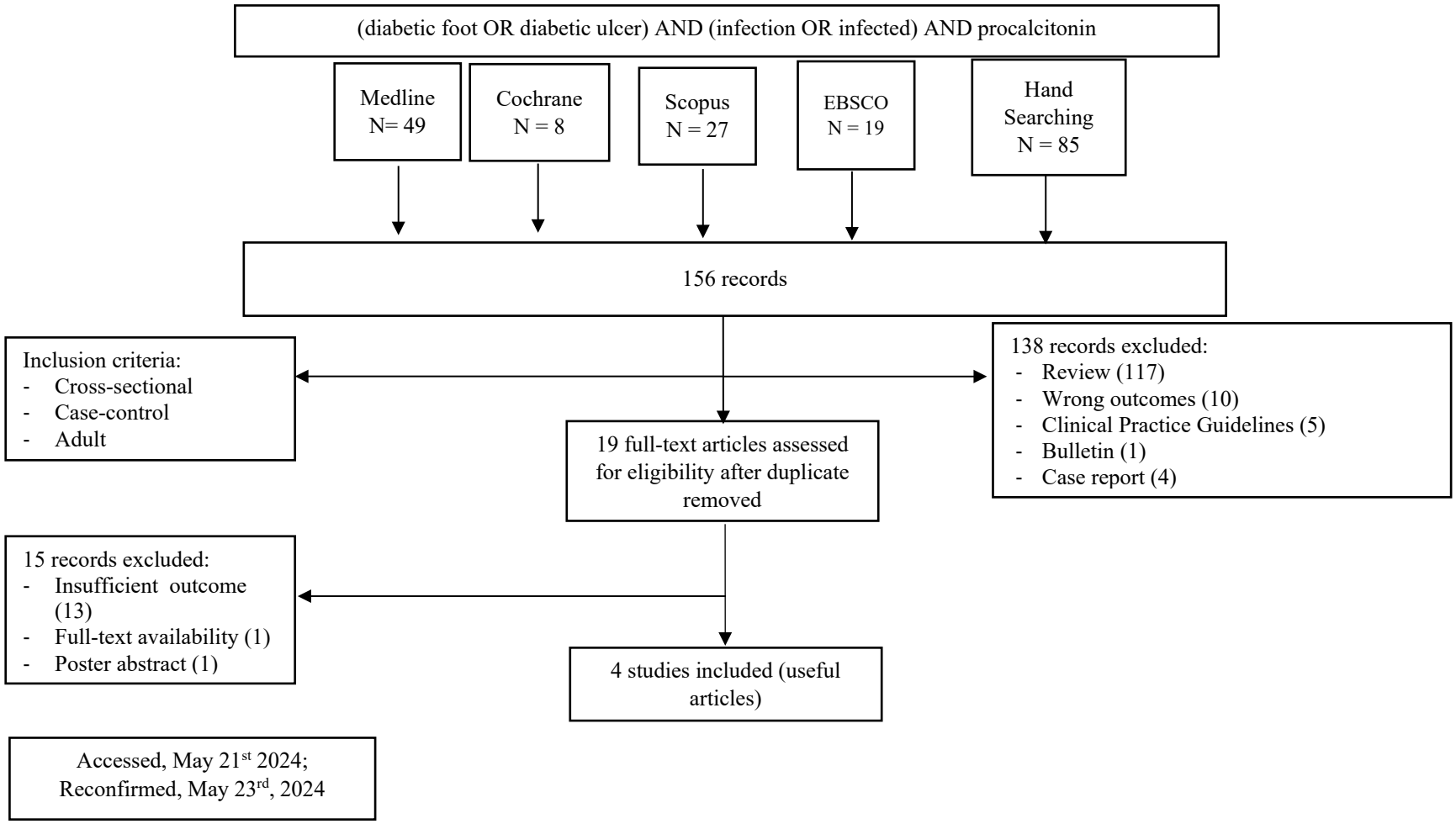

Figure 1. Flow Chart of Conducted Literature Searching

Table 2. Critical Appraisal of the Finding Studies

Author (Year)	Validity			Importance												Applicability
	The diagnostic test evaluated in a representative spectrum of patients	Reference test applied to all subjects regardless of the result	An independent, blind comparison between the index test and an appropriate reference	Cut off, ng/mL	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Likelihood Ratio (positive result)	Likelihood ratio (negative result)	Pretest probability	Pre-test odds	Post-test odds (LR positive)	Post-test odds (LR negative)	Post-test Probability	The methods for performing the test described in sufficient detail to permit replication
Jafari MJ, et. al. (2014)[4]	YES	YES	YES	0.21	70	74	70	50	2.6	0.4	0.5	1	2.6	0.4	0.72	YES
				0.5	61	53	26	83	1.3	0.62	0.5	1	1.3	0.62	0.56	
Al-Shammaree SAW, et. al (2017)[7]	YES	YES	YES	0.6	87.5	86.7	54.2	50	6.58	6.93	0.54	1.17	7.67	8.1	0.88	YES
Umapathy, et. al. (2018)[5]	YES	YES	YES	0.5	54	100	100	12	~	2.17	0.69	2.2	~	4.7	~	YES
Uzun, et. al. (2007)[3]	YES	YES	YES	0.06	78	73	78	73	2.8	3.3	0.55	1.2	3.4	3.96	0.78	YES
				0.08	77	100	100	78	~	4.34	0.55	1.2	~	5.2	~	
				0.1	59	100	100	67	~	2.43	0.55	1.2	~	2.92	~	

Table 3. The Summary of Evidence

Reference	Study Design	Subjects	Inclusion criteria	Exclusion criteria	Findings	Level of evidence
Jafari MJ, et al. (2014)[4]	Case-control	30 IDFU* 30 NIDFU** 30 controls	Clinicians (infectious diseases expert) diagnosed IDFU according to the IDSA guidelines. Clinically, IDFU (or grade ≥ 2 of IWGDF) was identified by the presence of purulent discharges or at least two of the features of inflammation including warmth, redness, swelling or induration, and pain or tenderness. NIDFU in the IDSA classification was characterized as grade I of the IWGDF.	Patients with other infectious diseases like sepsis, urinary tract infection, pneumonia, meningitis, patients admitted due to surgery in the previous six weeks, with malignancy, with inflammatory diseases such as inflammatory bowel syndrome, rheumatoid arthritis or other rheumatologic disorders, patients receiving immunosuppressive treatment and with previous use of antibiotics during the last 6 months were excluded from the study.	The PCT level was significantly higher in IDFU group than others.	4
Al-Shammaree SAW, et al. (2017)[7]	Case-control	16 controls 17 DM*** without DFU**** 25 NIDFU 30 IDFU	Patients with DFU were split into two groups according to IDSA-IWGDF criteria. Clinical signs of infection that recorded in this study were redness, swelling of the wound, pus spots, or exudates from the wound, fever, and pain in the infected area.	Patients, who receive antibiotic treatment for < 10 days or with any other source of infection, have been excluded from the study.	PCT levels were significantly higher in the infected DFU group when compared to other groups.	4
Umapathy, et al. (2018)[5]	Cross-sectional	75 without DFU 34 NIDFU 76 IDFU	Well-trained podiatrist defined the grade of diabetic ulcer infection. Microbiological report confirmed the infected wounds and classified as infected (grade > 2) or non-infected (grade 1) Patients with a positive bacterial culture and minimal clinical signs were followed up for one month to establish the status of the wound; if the infection was still found to be prominent, the wound was classified as IDFU.	Subjects with type 1 diabetes, gestational diabetes, pneumonia, sepsis, inflammatory bowel disease, meningitis, or hematologic diseases and those who underwent surgery in the past 2 to 3 weeks were excluded from this study. Those who refused to participate or withdrew their consent were also excluded.	PCT levels were significantly higher in the infected DFU group and there is 7-fold of the increasing level compared with NIDFU.	2B

Uzun, et al. (2007)[3]	Case-control	27 IDFU 22 NIDFU 22 control	Patients were evaluated for DFI by a medical team, (included an infectious diseases expert, a microbiology expert and an internal disease expert). These physicians were blinded to the biochemical analysis. DFI diagnosis was performed according to IDSA-IWGDF. DFI was diagnosed clinically by the presence of purulent secretions or at least 2 of the symptoms of inflammation including redness, warmth, swelling or induration, and pain or tenderness.	Patients with other infectious diseases such as sepsis, meningitis, inflammatory intestinal disease and pneumonia, patients who had undergone surgery in the previous six weeks, patients with hematological malignancy known to raise PCT levels, and patients receiving systemic immunosuppressive treatment were excluded from the study.	The PCT levels in IDFU group were significantly higher than those in the NIDFU	4

* IDFU: Infected Diabetic foot ulcer

** NIDFU: Non-infected Diabetic foot ulcer

*** DM: diabetes mellitus

**** DFU: diabetic foot ulcer

Discussion

IDSA/IWGDF gave criteria to classify the infected and non-infected diabetic ulcers. This simple method, as part of the full assessment of diabetic foot using PEDIS classification, defined the presence and severity of infection which could lead us to decide the aggressiveness of our therapy.[8] However, this method is quite challenging for those who are not expert in the diabetic foot, therefore all the finding studies[3–5,7] used trained physician or podiatrist. However, the only study conducted by Umapathy et al.[5] used microbiological reports as a confirmation of infection in diabetic foot ulcer. This confirmation method may reduce the bias and subjectivity of the assessor.

Proper specimen collection is essential to provide sufficient data. Deep tissue samples from curettage or tissue scraping from the base of ulcer are preferred over wound swab to reveal the true flora, which later may only provide colonizing agents providing false results. The proper spesimen, then cultured using selective or standard growth media, along with antimicrobial sensitivity testing. However, microbiological culture still have some disadvantages, including the fact that they take at least a couple of days to process, miss some facultative organisms, and are less useful in patients receiving antibiotic therapy.[3,10] On the other hand, the microbiological report may not only confirm the diagnose of infections but also provide definitive and sufficient antibiotics for our patients, especially they who are infected with multi-drug resistant organism (MDRO).

Procalcitonin has a vital role in helping the diagnosis of bacterial infections. PCT, released from the thyroidal C cells is the precursor of calcitonin.[1] Serum procalcitonin levels rises rapidly in response to systemic inflammatory insults, with peak levels that correlate with the intensity of the stimulus of cytokines produced by bacterial endotoxins.[3,10] On the other hand, its production is blocked by interferon-gamma, a cytokine released in response to viral infections. Procalcitonin has a short half-life (25–30 hours), and its peak in the serum is identified within 24 hours.[1,10] Then, its levels start to decline following effective treatment.[11]

Procalcitonin has been used in many countries and approved by the US Food and Drug Administration (FDA) as a diagnostic aid for sepsis in 2005. Its serial use to assess sepsis progression and 28-day mortality risk is also indicated by the FDA.[12]

Several studies have been found this biomarker level was significantly different between two groups, infected and non-infected diabetic foot.[3–7,13–16] However, only a few of them found procalcitonin has a good performance as a diagnostic aid.[3–5,7]

Several cuts off have been proposed to distinguish infected and non-infected diabetic ulcers. Jafari et. al.[4] and Al-Shammare, et. al.[7] found 0.21 and 0.6 as the cut off value of PCT level. However, both of them had a lower specificity compared with other reports.

Uzun et. al.[3] found 0.08 and 0.1 as a cut off which performed good specificity and sensitivity. On the other hand, Umapathy et al.[5] which had better quality level of evidence, reported higher cut off which has a good performance. The PCT value higher than 0.5 indicated the diabetic ulcer had been infected. This cut off may guide us to start antibiotics administration. Rhee[17] found 0.25 quite enough as a marker to start antibiotics in stable patients with respiratory infection. In critically ill patients, cut off 0.5 might be used as guidance to start antibiotics.[17] Moreover, Bouadma et. al.[12,18] found patients with less than 0.25 strongly discouraged from antibiotics use and patients which has procalcitonin more than one strongly encouraged with antibiotics used.

However, some studies found the opposite results. Korkmaz[19], Ingram[2], and Osquee[20] found there is no significant difference in PCT level between infected and non-infected diabetic ulcers. A systematic review may help to conclude this different result.

The early findings of diabetic foot infections give some benefits to give prompt antibiotics to prevent systemic infections and lower limb amputations as well as to reduce the morbidity and mortality rate.[2] PCT, compare with other biomarkers, can be detected within 4-6 hours after the onset of a bacterial infection, faster than C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[1,10] As a diagnostic tool, conflicting results arouse. Uzun[3] declared the AUROC of PCT for bacterial infections was the greatest one (0.859; $p<0.001$) followed by WBC (0.785; $p=0.001$), ESR (0.752; $p=0.003$) and CRP (0.625; $p=0.137$). Umapathy[5] found the same thing which area under the curve (AUC) was 0.99 for PCT, 0.78 for CRP, 0.76 for WBC count, and 0.74 for ESR. Both Jafari[4] and Al Shammaree[7] placed ESR at the top of the best area under the ROC curve compared with other inflammatory markers. PCT was at the third rank after CRP but still superior to WBC.

A meta-analysis by Majeed, et al.[21] revealed the sensitivity and specificity for ESR were calculated to be 0.84 (95% CI 0.76-0.89) and 0.82 (95%CI 0.73-0.89) with AUROC of 0.90 (95% CI 0.87-0.92). Pooled sensitivity and specificity for CRP were found to be 0.64 (95%CI 0.46-0.80) and 0.87 (95%CI 0.75-0.93) with AUROC of 0.85 (95% CI0.82-0.88). Pooled sensitivity and specificity for PCT were 0.74 (95%CI 0.62-0.83) and 0.93 (95%CI 0.65-0.99) with AUROC of 0.84 (95%CI 0.81-0.87).

Therefore, PCT could help rule in DFI in patients who have a high suspicion of disease; otherwise, ESR could be beneficial in ruling out diabetic foot infection in patients with a low

suspicion of disease.[21] However, this meta-analysis only published in poster format. The full-text of this systematic review was not published yet; thus we cannot appraise this meta-analysis comprehensively and include it in as evidence for this report.

Park, et al.[16] also reported among other biomarkers, only PCT could differentiate diabetic foot infections only with concurrent infections. When it combined with CRP values, they may help in the early distinction between grade 1 and 2 DFU (non-infected from mildly infected). AUROC for the combination of PCT and CRP (0.947±0.029) was significantly higher than that of either biomarker alone ($p<0.05$) in the distinction between grade 1 and grade 2 ulcers.[6] The performance of procalcitonin itself in that situation was not established.

Procalcitonin itself has several limitations. A positive result can arise in medullary carcinoma of the thyroid. Systemic inflammation, such as severe trauma, circulatory shock, surgery, burns, inhalation injury, and pancreatitis, can also elevate procalcitonin levels, possibly through gut translocation of lipopolysaccharide or other bacterial products.[10] False negatives can also occur, notably in contained localized infections such as mediastinitis, empyema, or abscesses, or if procalcitonin is drawn too early in the course of infection.[12]

Moreover, procalcitonin levels are significantly higher in culture-positive sepsis other than culture negative-sepsis. Also, in critically ill patients with microbiologically documented infection, procalcitonin levels differ by site of infection, with the highest levels in those with positive blood cultures and lowest with pulmonary cultures.[17] Lastly, procalcitonin did not give additional value to determine whether the ongoing infections still existed in diabetic ulcer.[22]

The limitation of the finding studies is they did not adjust the value of procalcitonin in infected groups according to the degree of the infections. The significant different PCT level between infected and non-infected groups can be contributed by the patients who had more severe infections, including osteomyelitis and bone involved infections. The more severe the infections, the higher procalcitonin level will be.[16] Thus, research which specifically revealed the benefit of procalcitonin level to distinguish non-infected and mildly infected diabetic foot might more beneficial for clinicians. Moreover, the studies recruited small number of subjects and had low quality level. A comprehensive systematic review is needed to overcome this limitation.

Lastly, the inflammatory marker such as procalcitonin has a costly price so that the examination should be done to selected patients. Not all patients with diabetic foot ulcer are needed this laboratory examination. Diagnostic infection assays, including non-specific testing of inflammatory markers, are likely to be most effective when combined with optimal clinical assessment and patient communication.[2]

Conclusion

Procalcitonin could be used to rule in patients with high suspicion disease of diabetic foot infections. As a diagnostic tool, PCT helps increase the pretest probability of infection. The best cut-off value was 0.5 with the 54 % sensitivity and 100 % specificity. However, procalcitonin is an additional tool to help clinicians overcome their clinical problem. linical feature still becomes the significant aspects which guide us to perform appropriate examination tool. IDSA-IWGDF criteria may be used as a diagnostic tool for diabetic foot infections. Moreover, a microbiological examination should be used as a confirmation tool. Also, a systematic review should be conducted to synthesize the conflicting results found in several studies and the small number of subjects recruited in finding studies.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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