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Original Article

Surgery Section

Effectiveness of Procalcitonin as a Diagnostic Marker vs Other Inflammatory Markers in Infected Diabetic Foot Ulcers: A Case-control Study

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ABSTRACT

Introduction: Procalcitonin (PCT), is an amino acid protein precursor of calcitonin hormone, which is released by thyroid parafollicular cells or other body cells. Procalcitonin alone or along with other biomarkers of infection such as erythrocyte sedimentation rate(ESR) and C-reactive protein (CRP) can be used as a marker for diagnosing diabetic foot infection.

Aim: To determine the effectiveness of PCT, as a marker for infected Diabetic Foot Ulcer (DFU) in comparison with other inflammatory markers such as CRP, White Blood Cell count (WBC), and ESR.

Materials and Methods: This case-control study was conducted at Department of General Surgery, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India from January 2018 to December 2018. Total 90 patients were classified into three groups with 30 patients in each group: group I had patients with diabetes but without foot ulcers while group II patients having Non infected DFU (NIDFU) and group III patients having Infected Diabetic Foot Ulcer (IDFU) served as cases. The parameters assessed were demographic data, blood pressure, Body Mass Index (BMI), diabetic complications like nephropathy, retinopathy and myocardial ischaemia and inflammatory markers.

Results: The mean age in group I was 46.9±5.11 years., group II was 47.8±6.65 years and in group III was 49.3±7.83 years. The gender distribution were group I (male 19, female 11), group II (male 13, female 17), group III (male 14, female 16). Serum PCT levels were 1.43±0.52 ng/mL in group III versus 0.18±0.17 ng/mL and 0.08±0.05 ng/mL in group II and group I respectively, with a significant p-value of 0.001. The PCT levels was significantly higher in patients with IDFU compared with the traditional markers like CRP (53.8±16.4 mg/dL, p-value=0.001), ESR (49.0±9.24 mm/hr, p-value=0.034) and WBC (10.2±3.18×10^9 / dL, p-value=0.014).

Conclusion: It was concluded that PCT, as a vital biochemical parameter, has an significant role to diagnose the infection in DFU as compared to CRP, WBC count and ESR.

Keywords: Amputation, Calcitonin, C-reactive protein, Diabetes mellitus

INTRODUCTION

Diabetic foot infection is an increasing problem in the developing world with a prevalence of 5.5% (95% CI: 4.6 %-6.4%). Progression of infection; may lead to increased chances of hospitalisation of the patients, surgical intervention and amputation [1-3]. Unfortunately, the quality of life in lower limb amputated patients is quite poor [4,5].

Therefore, diabetic foot wound needs careful assessment for presence of infection and classification of the severity of the infection when present. Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF), is a clinical classification system where the infected DFU (IDFU) is classified as mild (restricted involvement of one's skin and subcutaneous tissues), moderate (more extensive or affecting deeper tissues) and severe (accompanied by systemic signs of infection or metabolic instability) [6,7]. These classification schemes are effective and helpful for their prognosis and assessment of need of amputation in patients with diabetic foot [8].

Diagnosis of IDFU depends on size and depth of the wound, involvement of the underlying bone and presence of sinus tract, amount of pus discharge from the wound and active signs of inflammation around the ulcer [9]. Infection can markedly deteriorate patient's condition, so it is important to diagnose IDFU early [10]. Procalcitonin (PCT) is the precursor of calcitonin hormone synthesised by parafollicular C-cells in the thyroid gland [11]. PCT production by blood mononuclear cells increases after inflammation and is modulated by lipopolysaccharides and cytokines during sepsis [12].

Routine inflammatory markers like CRP, ESR and WBC can be used for diagnosing systemic infection. However, PCT is superior to the routine inflammatory markers in the diagnosis of both systemic and localised bacterial infections [13,14]. Study by Jeandrot A et al., [15] has shown that PCT has limited role in the discrimination of degrees of severity of diabetic foot infections. However, only a few studies are there in literature like those of Uzun G et al., Massara M et al., and Umapathy D et al., about the value of PCT levels in diagnosing localised infections [16,17,18]. Hence, present study was conducted to determine the usefulness of PCT as a marker for diagnosing infection in DFU in comparison with other routine inflammatory markers like CRP, ESR and WBC.

MATERIALS AND METHODS

This case-control study was conducted at Department of General Surgery, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India from January 2018 to December 2018. The protocol for this study followed the ethical standards and was approved by the Ethical Committee of the Institution (ECR/307/KIMS/Inst/Kar/2013). All patients gave informed written consent to participate in this study.

Inclusion criteria: Diabetic patients with IDFU and NIDFU were taken as cases. Age and sex matched diabetic patients, without DFU were taken as controls. IDFU diagnosis was based on IDSA-IWGDF classification of foot infections [7]. NIDFU diagnosis was made when the ulcer was small and covered with healthy granulation tissue, was superficial without bone or tendon involvement and no signs of active inflammation like redness, swelling, tenderness and local rise of temperature [17].

Exclusion criteria: Patients with active inflammatory bowel disease, pneumonia, meningitis, gestational diabetes, and who underwent any form of surgery in the past 2-3 weeks were excluded.

Sample size calculation: Considering the prevalence of Diabetic Foot Ulcer at KIMS hospital, Bangalore to be 2%, the sample size was calculated using the formula

$S=Z^2PQ/D^2$

Where S=Sample size; Z=Standard value at 0.05 level=1.96; P=Proportion of prevalence=2% becomes 0.02; Q=1-P=1-0.02=0.98; D^2=Margin of error or CI=5%=0.05 (to be expressed in decimals)

S=(1.96×1.96×0.02×0.98)/0.05×0.05=30/group.

The power of the study was 80% and above with α error of 0.05.

Total 90 patients were classified into three groups-

- Group I (Controls) (n=30)- Patients with diabetes but without foot ulcers.
- Group II (Cases) (n=30)- Patients had NIDFU.
- Group III (Cases) (n=30)- Patients had IDFU.

Data collection: Thorough history and clinical examination including measurement of blood pressure, weight, height and BMI was done in every patient as they are risk factors for poor outcome. Diabetic complications (retinopathy, nephropathy, and cardiovascular diseases) were documented for all groups. Complete blood count, inflammatory markers (PCT, ESR, and CRP), Fasting Blood Glucose (FBS), 2hr Postprandial Blood Glucose (PPBS), glycated haemoglobin (HbA1c), kidney functions (urea and creatinine), and lipid profile (total cholesterol, triglycerides, and Low-Density Lipoprotein (LDL) cholesterol) were done before the eventual initiation of antimicrobial treatment in all patients who were included, as they have negative influence on clinical outcome.

HbA1c (6.0% to 6.5%), lipid profile (total cholesterol less than 200 mg/dl, Triglycerides less than 150 mg/dl, LDL less than 100 mg/dl) and kidney function (blood urea nitrogen 14-23 mg/dl and serum creatinine 0.7-1.3 mg/dL) [19] were carried out by Dimension RxL Max analyser (Siemens Health GmbH-Henkestr, Erlangen, Germany) by colorimetric techniques. HbA1c percentages were determined by using cation exchange resin. For analysing the PCT levels, blood samples with a volume of 0.5 mL were collected and centrifuged for 20 min at 4000 rpm. The serum PCT levels were tested using Enzyme-Linked Immunosorbent Assay (ELISA) technique kit (Chongqing Biospes, Chongqing, China), with a reference value in adult is less than 0.1 ng/ml and levels greater than 0.25 ng/ml indicate presence of infection. The biochemical tests for the various parameters and their normal reference range are shown in [Table/Fig-1].

Parameters	Biochemical test method	Normal reference range [19]
Blood urea	Urease	17-43 mg/dL
BUN	Calculation-urea /2.14	14-23 mg/dL
Creatinine mg/dl	Modified Jaffe's	0.7-1.3 mg/dL
HbA1c	Cation exchange resin	6.0%-6.5%
Lipid Profile	Enzymatic assays	Total Cholesterol <200 mg/dL Triglycerides <150 mg/dL LDL Cholesterol <100 mg/dL
PCT	ELISA kit	<0.1 ng/mL (>0.25 ng/mL-presence of infection)
ESR	Westergren	0 to 22 mm/hr (male) 0 to 29 mm/hr (female)
CRP	ELISA kit	<10 mg/L

[Table/Fig-1]: Biochemical tests for various parameters with their normal reference range.
*BUN: Blood urea nitrogen; †HbA1c: Glycated hemoglobin; §PCT: Procalcitonin; **ESR: Erythrocyte sedimentation rate; ††CRP: C reactive protein; Enzyme -linked Immunosorbent Assay; Low-density lipoprotein

STATISTICAL ANALYSIS

Data entry, coding, and analysis were assessed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, New York, USA). Description of quantitative variables were in the form of mean±SD. One-way analysis of variance test or Kruskal-Wallis test was used as appropriate for comparison of quantitative variables between more than two independent groups. Multiple stepwise regression analysis was done to determine the possible predictor for infection in DFU between potential risk factors including inflammatory markers. A p-value up to 0.05 was considered significant.

RESULTS

The mean age was 46.9±5.11, 47.8±6.65 and 49.3±7.83 years, among group 1, group 2 and group 3 respectively. The demographic data (mean age, gender), clinical data (BMI and BP) and diabetic co-morbidities (nephropathy, retinopathy and CVS diseases) did not show any statistically significant difference among the study groups. [Table/Fig-2].

The fasting blood sugar, 2hr post prandial blood sugar, triglycerides, serum creatinine, haemoglobin and platelets showed statistically significant difference between the study groups (p-value≤0.05). However, there was no statistically significant difference with respect to total cholesterol, LDL-C, HbA1c and blood urea amongst the study groups [Table/Fig-3].

Variables	Groups (n=30)			Test of significance	p-value
	Group I	Group II	Group III		
Age (mean±SD) (years)	46.9±5.11	47.8±6.65	49.3±7.83	0.97[a]	0.380
Gender [n(%)]					
Male	19 (63.3)	13 (43.3)	14 (46.7)	2.75[b]	0.252
Female	11 (36.7)	17 (56.7)	16 (53.3)		
Blood pressure (mean±SD) (mmHg)					
SBP	126.4±17.5	127.3±12.8	130.1±11.3	0.784[a]	0.460
DBP	80.3±6.69	80.4±7.42	82.2±6.75	0.518[a]	0.597
BMI (mean±SD) (kg/m^2)	26.4±3.05	27.5±3.25	27.3±2.44	1.06[a]	0.348
Co-morbidities [n(%)]					
Nephropathy	10 (33.3)	12 (40)	15 (50)	3.45[b]	0.968
Retinopathy	6 (20)	4 (13.3)	5 (16.7)		
Nephropathy and retinopathy	4 (13.3)	3 (10)	3 (10)		
Myocardial ischaemia	5 (16.7)	4 (13.3)	4 (13.3)		
Coronary artery disease	3 (10)	4 (13.3)	2 (6.70)		
Cardiovascular disease	2 (6.70)	3 (10.0)	1 (3.30)		

[Table/Fig-2]: Demographic and clinical data of the studied groups (N=90).
§DBP diastolic blood pressure; **SBP systolic blood pressure; p-value>0.05 NS Analysis of variance test bX2 Test; BMI: Basal metabolic index

Variables	Groups (Mean±SD) (n=30)			Test of significance	p-value	Post-hoc test
	Group I	Group II	Group III			
Fasting blood glucose (mg/dL)	137.9±24.7	151.8±36.0	155.9±24.4	3.19[a]	0.046	P_1: 0.066 P_2: 0.018* P_3: 0.581
2hr postprandial blood glucose (mg/dL)	211.7±26.3	229.2±30.2	230.3±29.5	4.03[a]	0.021	P_1: 0.020* P_2: 0.013* P_3: 0.7851
HbA1c (%)	8.11±0.60	8.45±0.72	8.53±0.95	1.62[a]	0.204	P_1: 0.089 P_2: 0.190 P_3: 0.689
Total cholesterol (mg/dL)	236.6±19.1	233.4±20.1	243.4±20.9	1.95[a]	0.148	P_1: 0.558 P_2: 0.193 P_3: 0.056
Triglycerides (mg/dL)	208.9±33.4	209.9±34.3	227.1±32.8	3.89[a]	0.067	P_1: 0.907 P_2: 0.015* P_3: 0.051
LDL-C (mg/dL)	121.6±22.4	129.2±24.2	131.1±25.2	1.30[a]	0.278	P_1: 0.224 P_2: 0.132 P_3: 0.768
Urea (mg/dL)	32.0±5.21	33.3±5.48	34.7±5.88	1.74[a]	0.181	P_1: 0.353 P_2: 0.065 P_3: 0.352
Creatinine (mg/dL)	1.21±0.25	1.23±0.29	1.40±0.35	3.48[a]	0.035	P_1: 0.832 P_2: 0.019* P_3: 0.043
Hemoglobin (g/dL)	11.2±1.32	10.6±1.01	10.3±1.46	3.40[a]	0.038	P_1: 0.077 P_2: 0.012* P_3: 0.254
Platelet (x10^9/L)	277.7±68.2	297.3±64.1	325.7±83.0	3.34[a]	0.040	P_1: 0.297 P_2: 0.012* P_3: 0.132

[Table/Fig-3]: Laboratory investigations among the studied groups (N=90).
*HbA1c, glycated hemoglobin; †IDFU, infected diabetic foot ulcer; §NIDFU, noninfected diabetic foot ulcers. [a]Analysis of variance test. P_1: Comparison between control group and NIDFU group. P_2: Comparison between control group and IDFU group. P_3: Comparison between NIDFU group and IDFU group. *Significant

The levels of inflammatory markers like ESR (p-value=0.034), WBC (p-value=0.014), CRP (p-value=0.001) and PCT (p-value=0.001) were significantly higher in patients of group III as compared to patients in group I and II [Table/Fig-4].

Multivariate logistic regression analysis was done to identify the predictable factors for infection among patients with diabetic ulcer. This showed that elevated levels of CRP (p-value=0.026, 95% CI: 1.04%-1.16%) and PCT (p-value=0.001, 95% CI: 31.3%-79.0%) were significant inflammatory markers that predicted the presence of infection in patients of group III as compared to patients in group I and II. [Table/Fig-5].

The Receiver Operating Characteristic curve analysis of inflammatory markers for detection of infection was done among patients with DFU. PCT had higher Area Under Curve (AUC), sensitivity, specificity and accuracy more than CRP concentration, WBC count and ESR levels correspondingly. [Table/Fig-6,7].

Variables	Groups (Mean±SD) (n=30)			Test of significance	p-value	Post-hoc test
	Group I	Group II	Group III			
WBC (x10^9/L)	8.22±2.19	6.66±2.57	10.2±3.18	4.48[a]	0.014	P_1: 0.530 P_2: 0.005* P_3: 0.029
ESR (mm/h)	40.9±10.1	43.0±12.1	49.0±9.24	3.51[a]	0.034	P_1: 0.438 P_2: 0.011* P_3: 0.035*
CRP (mg/dL)	26.2±8.52	34.6±11.5	53.8±16.4	41.5[b]	0.001	P_1: 0.010* P_2: 0.001** P_3: 0.001**
PCT (ng/mL)	0.08±0.05	0.18±0.17	1.43±0.52	63.0[b]	0.001	P_1: 0.002 P_2: 0.001** P_3: 0.001**

[Table/Fig-4]: Inflammatory markers among study groups (N=90).
*CRP: C-Reactive protein; †ESR: Erythrocyte sedimentation rate; §IDFU: Infected diabetic foot ulcer; **NIDFU: Noninfected diabetic foot ulcer; †PCT: Procalcitonin; WBC: White blood cell; aAnalysis of §†§§ variance test; bKruskal-Wallis test; P_1: Comparison between control group and NIDFU group; P_2: Comparison between control group and IDFU group; P_3: Comparison between NIDFU group and IDFU group; *p-value=0.05 significant, **p-value=0.001 highly significant

Predictors	β	Wald	p-value	95% CI
WBC (x10^9/L)	0.19	3.80	0.051	0.99-1.47
ESR (mm/h)	0.04	2.95	0.085	0.99-1.09
CRP (mg/dL)	1.12	4.97	0.026*	1.04-1.16
PCT (ng/mL)	8.51	10.3	0.001**	31.3-79.0

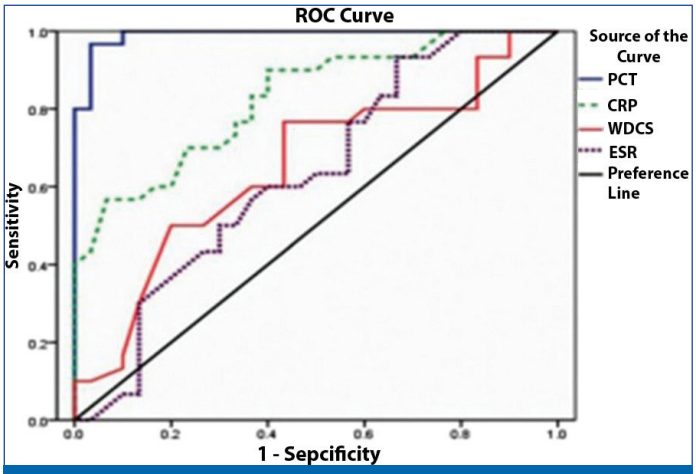
[Table/Fig-5]: Multivariate logistic regression analysis to detect predictable factors for infection among patients with diabetic ulcer.
*CI: Confidence interval; †CRP: C Reactive protein; §ESR: Erytrocyte sedimentation rate; **PCT: procalcitonin; ††WBC: White blood cell; *Significant difference; **Highly significant

DISCUSSION

Diabetic foot infection and ulcers are common complications of diabetes mellitus with a difficult prolonged healing process and chronic pattern [20]. Diabetic complications such as peripheral neuropathy, peripheral vascular disease, and abnormal foot position predispose to DFUs, which may be infected in the presence of abrasion and deeper tissues such as the underlying bone may be involved [21].

Inflammatory markers	Area under curve	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PCT	0.946	0.60	93	83	85	93	88
CRP	0.827	38.5	83	63	69	79	73
WBCs	0.651	8.70	77	57	64	64	67
ESR	0.631	40.5	77	40	56	63	58

[Table/Fig-6]: Receiver operating characteristic curve analysis of inflammatory markers for detection of infection among patients with diabetic ulcer (N=90).
p-value P_1: comparison between PCT and CRP (0.007); P_2: comparison between PCT and WBCs (0.001); P_3: comparison between PCT and ESR (0.001)
*AUC: Area under the curve; †CRP: C reactive protein; §ESR: Erythrocyte sedimentation rate **NPV: Negative predictive value; ††PCT: Procalcitonin; §§PPV: Positive predictive value; ***WBC: White blood cell



[Table/Fig-7]: Receiver operating characteristic curve represents the specificity and sensitivity of inflammatory marker (PCT, CRP, ESR, and WBC) for detection of infection among group III.
*CRP: C: Reactive protein; †ESR: Erythrocyte sedimentation rate; §PCT, Procalcitonin; **WBC, white blood cell

Diagnosis of IDFU is usually clinical [17]. PCT is produced in direct response to bacterial endotoxins and indirectly to mediators such as interleukin (IL)-1β, tumour necrosis factor-α, and IL-6, and it is strongly correlated with severity of infection [22,23]. Low Haemoglobin, FBS, PPBS and altered lipid profile can adversely influence the overall health of the patient. Deranged Renal function tests (RFT) can be a complication of diabetes, which in turn influences the poor outcome in these patients [17].

Though the diagnosis of IDFU is most often clinical, inflammatory markers such as CRP, WBC count, ESR and PCT may help to diagnose IDFU when the clinical signs are misleading. Serum PCT levels vary based on the site and extent of infection. Mean PCT concentration (in ng/ml) in group I, II and III was 0.08±0.05, 0.18±0.17 and 1.43±0.52 respectively. Significantly higher levels of PCT (p-value=0.001) were found in patients with IDFU. Uzun G et al., and Massara M et al., also demonstrated the higher efficiency of PCT in diagnosing IDFU [16,17].

Serum CRP, being an acute phase reactant protein, increases during inflammatory processes and is higher in diabetic patients as compared to healthy subjects. However, their levels increase significantly in the presence of localised or systemic infection in patients with IDFU. This is further reiterated by the finding in the present study where mean CRP levels of 53.18±16.14 mg/dl was significantly higher (p-value= 0.001) in patients with IDFU as compared to patients with NIDFU (34.0±11.5 mg/dl). Similar findings were also noted by Massara M et al., Umapathy D et al., and Park JH et al., [17,18,19]. Total WBC count has been accepted as a universal marker of infection and significantly higher levels of WBC count (p-value=0.014) was found in patients in group III (IDFU) as compared to patients in group I and II. Though ESR was also elevated in patients with IDFU, it had the lowest statistical significance (p-value=0.034) compared to other inflammatory markers. Studies has shown that the levels of PCT are correlated well with the grade of IDFU [18,22]. PCT levels start rising by 4 hrs after a bacterial infection and peak levels are found between 6 to 24 hrs; whereas the CRP levels start rising after 12-24 hrs and peak levels are found after 48 hrs of bacterial infection [18]. Therefore, measurement of PCT levels may help in the early diagnosis, management and prevention of complications of IDFU like amputation and death of patients. The combination of PCT and CRP levels was more sensitive in identifying infection among patients with DFU as reported by Jeandrot A et al., [15]. Combining the measurements of CRP and PCT increased the accuracy of predicting wound infection. Highest sensitivity was obtained when the two markers such as PCT and CRP were considered together to distinguish IDFU from NIDFU.

In this study, the AUROC for PCT was 0.946 as compared to other traditional markers like CRP (0.822), WBC count (0.651) and ESR (0.631). Also, at a cut-off value of 0.60 ng/ml PCT levels had sensitivity, specificity, PPV, NPV and accuracy of 93, 83, 85,93 and 88% respectively. Similarly, Umapathy D et al., [18] found that, at a cut-off value of 0.50 ng/mL, PCT had a AUROC, sensitivity, specificity, PPV, NPV and accuracy of 0.99, 54, 100, 100, 12 and 95% respectively. In contrast to the findings of Uzun G et al., Massara M et al., Umapathy D et al., and the present study, Jafari N et al., found that ESR and Jeandrot A et al., found that CRP was the most sensitive inflammatory marker to distinguish IDFU and NIDFU [14-18]. Since PCT and CRP were more predictable of infection, these two parameters were compared with respect to cut-off value, AUROC, sensitivity, specificity, PPV and NPV with other studies[14-16,22] and tabulated as shown in [Table/Fig-8].

Limitation(s)

First, the grading of infection severity of DFUs in this study depended on clinical examination guided by only IDSA-IWGDF clinical classification and interobserver variability difference in grading infection severity would have occurred. Second,

	Studies									
	Present Study		Jafari JN et al., Iran 2014 [14]		Jeandrot A et al., France 2008 [15]		Uzun G et al., Turkey 2007 [16]		Umapathy D et al., Chennai 2018 [18]	
Parameters	PCT	CRP	PCT	CRP	PCT+ CRP	CRP	PCT	CRP	PCT	CRP
Cut-off value	0.6	38.5	0.5	7.1	4	17	0.08	32.1	0.5	-
AUROC	0.946	0.827	0.729	0.871	0.947	0.893	0.859	0.625	0.99	0.78
Sensitivity	93	83	61	80	0.909(SD 0.061)	0.727(SD 0.099)	77	29	54	-
Specificity	83	63	53	74	0.826(SD 0.0079)	1.000(SD 0.043)	100	100	100	-
PPV	85	69	26	80	0.833(SD 0.079)	1.000(SD 0.052)	100	100	100	-
NPV	93	79	83	46	0.905(SD 0.064)	0.793(SD 0.079)	78	53	12	-

[Table/Fig-8]: Comparison of the diagnostic markers between the present study and other studies.
*PCT, Procalcitonin (ng/ml); †CRP, C Reactive protein(mg/dl); §PPV, Positive predictive value; **NPV, Negative predictive value; ††AUROC, Area under receiver operating curve

the PCT level was not correlated with age, type of pathogen isolated, site and type of infection more research studies are needed to evaluate the diagnostic validity of PCT in diagnosing IDFU patients.

CONCLUSION(S)

Procalcitonin levels were significantly elevated in patients with infected DFU compared to non infected DFU patients. Various complications associated with diabetes like peripheral neuropathy, peripheral vascular disease, diabetic nephropathy and parameters like low Hb, HbA1c, poorly controlled blood sugars and lipid profile can adversely influence the health of the patient. Inflammatory markers like PCT, CRP, WBC and ESR will be elevated in the presence of IDFU. In this study, PCT was significantly elevated compared to other inflammatory markers in patients with infected DFU as compared to non infected DFU. Hence this study concluded that PCT levels had higher efficiency in distinguishing between IDFU from NIDFU followed by CRP, WBC, and ESR levels.

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