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Serum Procalcitonin, Cystatin C, Kidney Injury Molecule-1 Levels in Patients with Diabetic Foot Ulcer and Relation with Chronic Kidney Disease

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Abstract

Objective: To evaluate the serum levels of Procalcitonin (PCT), C-Reactive Protein (CRP), Cystatin C, and Kidney Injury Molecule-1 (KIM-1) in patients with diabetic foot ulcers (DFU).

Methods: This case-control study included 120 participants divided into four groups: 30 with diabetic foot ulcers (DFU), 30 with diabetic foot ulcers and chronic kidney disease (DFU & CKD), 30 with diabetes mellitus (DM), and 30 healthy controls. The study was conducted from November 2023 to March 2024. Laboratory tests performed on all patients and controls included CBC, blood urea, serum creatinine, and serum CRP levels using a fully automated analyzer. PCT, Cystatin C, and KIM-1 levels were measured using the ELISA method.

Results: The biomarkers PCT, CRP, and WBC showed a significant increase in the diabetic foot group and the diabetic foot with chronic kidney disease group. Additionally, there were positive correlations between PCT and CRP and Cystatin C, and between KIM-1 and Cystatin C. ROC analysis of PCT demonstrated high sensitivity and specificity (91.1% and 99%, respectively).

Conclusions: Elevated Procalcitonin levels in diabetic foot patients can predict early infection even without clear clinical signs. Increased levels of Cystatin C and KIM-1 serve as good biomarkers for renal function and complications of diabetes, showing a close relationship with diabetic foot conditions.

Keywords: Procalcitonin, cystatin C, foot ulcer, diabetic, renal insufficiency, chronic

Introduction

Diabetic foot is one of the most serious complications of diabetes and can lead to foot amputation.[1] Chronic hyperglycemia, ischemia, and neuropathy are the primary risk factors for diabetic foot. Approximately 34% of diabetic patients (both Type 1 and Type 2) will develop a diabetic foot ulcer (DFU).[2] Multiple classification systems exist, such as the Infectious Diseases Society of America-International Working Group on the Diabetic Foot (IDSA-IWGDF), which categorizes diabetic foot based on the severity of the infection.[3] Early diagnosis of infected DFU is crucial because infections can significantly deteriorate a patient's condition.[4]

Procalcitonin (PCT) is the precursor of the hormone calcitonin, synthesized by parafollicular C-cells in the thyroid gland.[5] PCT is produced by blood mononuclear cells in response to inflammation and is modulated by lipopolysaccharides and cytokines during sepsis.[6] Elevated PCT levels are observed in DFU and are considered a marker of infection. In healthy individuals, PCT levels are typically low or undetectable in the absence of inflammation. PCT levels rise quickly during bacterial infections,[7] making PCT a suitable and specific biomarker, potentially replacing traditional markers such as CRP and WBC.[8] Despite PCT's accuracy in diagnosing infections compared to CRP, some studies report its limited role in assessing the severity of diabetic foot infections.[9] Another biomarker, Cystatin-C (Cys C), is considered an early predictor for diagnosing chronic kidney disease.[10] Cystatin C is produced in all human cells containing a nucleus and can predict cardiovascular disease progression. It is also implicated in neurological conditions like Alzheimer's disease.[11]

Kidney Injury Molecule-1 (KIM-1) is another potential biomarker that can be studied in DFU. KIM-1 serum levels are significantly higher in patients with sepsis compared to other critical illnesses,[12] and it is particularly elevated in cases of urogenital sepsis and liver failure. KIM-1 is a cell surface receptor involved in the phagocytosis of dying cells and is notably elevated in proximal tubules affected by acute kidney injury (AKI) and chronic kidney disease (CKD).[13] While there are limited studies on the combined use of PCT, Cystatin C, and KIM-1 in diagnosing infected DFU, exploring these biomarkers' potential associations with DFU could be beneficial. Therefore, we aim to clarify the usefulness of PCT, Cystatin C, and KIM-1 as biomarkers of infection in diabetic foot ulcers.

Materials and Methods

Study Design

An endocrinologist diagnosed all diabetic patients that were included in this study based on clinical findings and measurements of FBS and HBA1C. Most of the cases were collected from Marjan Teaching Hospital and Al-Hilla general teaching Hospital in Hilla city during the period from November 2023 to March 2024.The protocol for this study followed the ethical standards and was approved by the ethical committee of our institution, and all patients gave informed consent to participate in this study.

All participants (age from 32–68 years) in this study were divided into four groups, each group consisted of 30 people comprising diabetic mellitus patients without any complication, diabetic foot ulcer and diabetic foot with chronic kidney disease. Thirty people have been included as a control group (apparently healthy). The sample size was determined according to G power program for sample size determination.

Inclusion Criteria

Patients group whose age varied from 18 to 80 years, and who have undergone a clinical examination by endocrinologist and the control group was selected as apparently healthy individuals.

Exclusion Criteria

These include cancer patients, patients less than 18 years old, pregnancy, congestive heart failure, systemic lupus erythematous, and incomplete data were excluded from this study.

Blood Sampling

Venous blood was drawn from all participants using disposable syringes. The blood was discharged slowly and divided into two parts. The first was discharged into tube with anticoagulant, used in hematological tests like CBC and HBA1C. The second part was discharged into plain tubes, where the blood could clot before being centrifuged to separate the serum into two parts. The first was used right away for a routine test that included serum FBS, CRP, B. urea, and S. Cr. The second (serum) was kept in a deep freezer to be analyzed using the ELISA method for PCT, Cys C, and KIM-1.

Outcome Measurements

Fasting blood sugar, B. urea and S. Cr levels were analyzed by using fully automated chemistry analyzer Diriu device. The CBC device measured the blood markers WBC and Hb using an EDTA tube. The CRP and HBA1C were measured using Afias device that uses an immune assay technique.

Statistical Analysis

Statistical program (SPSS version 24.0) was used. A one-way analysis of variance (ANOVA) test was used to analyze the differences in variable means between the control and patient groups. The results were expressed as mean ± standard deviation (SD). Using Pearson's correlation coefficient (r), correlations between all variables under study were assessed, and data analysis methods included linear regression analyses. Statistics were deemed significant when the P-value was less than 0.05. The study variables' cut-off values, sensitivity, specificity, and area under the curve were displayed using the receiver operating characteristic (ROC) curve.

Results

General Characteristics of the Study

Age and body mass index in patients and controls

The study groups (Control, DM, DFU, DFU&CKD) had mean ± SD of ages and of BMIs, and their values are listed in Table 1. The patient groups (DM, DFU, and DFU & CKD) had significantly higher in mean ages but significantly decrease in mean of BMIs ($P > 0.05$) than the control group. Similar manners, the ages had higher, but BMIs had lower ($P > 0.05$) between the groups with diabetes mellitus compared with DFU and DFU & CKD groups. However there was no significant difference ($P < 0.05$) in mean of age between DFU group with DFU & CKD group. Similarly, a decrease ($P > 0.05$) in mean of BMI between DFU group compared DFU & CKD group.

Serum Level of B. Urea, S. creatinine and eGFR

There were increased significantly ($P < 0.05$) in mean levels of B. Urea in DM group compared with controls. On the other hand, there were high significant increases ($P < 0.01$) in mean of B.Urea in DFU group compared with controls. Similarly, B.urea levels were higher in DFU & CKD group than in controls ($P < 0.001$).

The mean of serum levels of s.cr showed no significant differences ($P > 0.05$) between control groups and DM group. In contrast, higher levels of s.cr was observed in DFU than in ($P < 0.01$) control group. While higher levels of s.cr was observed in DFU & CKD compared with controls, diabetic, diabetic foot ulcer groups $P < 0.001$) (Table 1).

There was high significantly decrease ($P < 0.001$) in mean of eGFR in control group compared with DM, DFU and (DFU & CKD) groups. In addition, there were significantly decreased ($P < 0.001$) when compared with the mean of eGFR in DM group compared with DFU and (DFU & CKD) groups and similarly was observed between DFU groups and DFU& CKD group.

Fasting Blood Sugar and HBA1C in Patients and Controls

In comparison to the control group, the mean HBA1C and FBS values were found to be significantly increased ($P < 0.001$)

Table 1. **The mean ± SD levels of biomarkers (age, BMI, B. urea, S.cr, eGFR, FBS, HBA1C)**

Parameters	Control mean ± SD $n = 30$	DM mean ± SD $n = 30$	DFU mean ± SD $n = 30$	DFU&CKD mean ± SD $n = 30$
Age years	48.93 ± 7.02	53.6 ± 6.1$^{a▲*}$	57.3 ± 3.4$^{a▲** b▲*}$	59.3 ± 4.03$^{a▲*** b▲** c=ns}$
BMI Kg/m^2	27.05 ± 2.22	25.1 ± 2.5$^{a▼*}$	24.1 ± 1.4$^{a▼* b▼*}$	22.3 ± 1.2$^{a▼** b▼* c▼*}$
B.Urea (mg/dl)	28.7 ± 5.6	34.4 ± 2.2$^{a▲**}$	38.03 ± 4.5$^{a▲** b=ns}$	100.9 ± 18.6$^{a▲*** b▲*** c▲***}$
S.Cr (mg/dl)	0.76 ± 0.13	0.84 ± 0.10$^{a=ns}$	0.9 ± 0.12$^{a▲* b=ns}$	2.9 ± 0.38$^{a▲*** b▲*** c▲***}$
eGFR (ml/min/1.73m^2)	109.6 ± 10.2	95.7 ± 10.4$^{a▼**}$	82.6 ± 13.5$^{a▼*** b▼**}$	21.4 ± 4.2$^{a▼*** b▼*** c▼***}$
HBA1C %	4.7 ± 0.44	10.3 ± 1.15$^{a▲***}$	12.9 ± 0.81$^{a▲*** b▲***}$	13.2 ± 0.69$^{a▲*** b▲*** c=ns}$
FBS (mg/dl)	102.3 ± 9.8	256.7 ± 29.6$^{a▲***}$	357.4 ± 17.9$^{a▲*** b▲***}$	363.7 ± 28.3$^{a▲*** b▲*** c▲*}$

N, Number: SD, Standard deviation: ▲, significant increase: ▼, significant decrease: *, (P<0.05): **, (P<0.01): ***, (P<0.001): ns, non-significant: a, ANOVA test between control: DM, DFU and DFU & CKD groups, b, ANOVA test between DM and DFU, DFU & CKD groups: c, ANOVA test between DFU and DFU & CKD groups.

Table 2. **The mean± SD of procalcitonin, CRP and WBC levels in all groups**

Parameters	Control mean ± SD n = 30	DM mean ± SD n = 30	DFU mean ± SD n = 30	DFU&CKD mean ± SD n = 30
Procalcitonin (ng/ml)	0.171 ± 0.049	0.287 ± 0.074$^{a▲*}$	1.449 ± 0.163$^{a▲*** b▲***}$	1.488 ± 0.221$^{a▲*** b▲*** c▲**}$
C-reactive protein (mg/dl)	4.4 ± 1.19	4.66 ± 0.82$^{a=ns}$	53.5 ± 16.6$^{a▲*** b▲***}$	77.0 ± 11.2$^{a▲*** b▲*** c▲***}$
WBC (cell/ml)	5.6 ± 1.2	6.03 ± 1.15$^{a=ns}$	13.9 ± 1.6$^{a▲*** b▲***}$	13.8 ± 1.3$^{a▲*** b▲*** c=ns}$

N, Number: SD, Standard deviation: ▲, significant increase: *, (P<0.05): **, (P<0.01): ***, (P<0.001): ns, non-significant: a, ANOVA test between control, DM, DFU and DFU &CKD groups: b, ANOVA test between DM and DFU, DFU & CKD groups: c, ANOVA test between DFU and DFU & CKD groups.

in the patient groups (DM and DFU, DFU & CKD) compared with controls. Similarly, there were significant increases (P < 0.01) in the HBA1C and FBS values in the DM group when compared to the DFU, DFU & CKD groups. When comparing the levels of HBA1C between the DFU group with the DFU & CKD group, we could not find any differences (P > 0.05) Table 1.

The level of mean ± SD Procalcitonin, CRP and WBC Levels in all Groups

The results of mean ± SD of Procalcitonin, C-reactive protein and WBC for control group and patients' groups (DM, DFU and DFU & CKD) are shown in Table 2. The means level of Procalcitonin was significantly higher in DM group, DFU, DFU & CKD compared with normal controls. (0.287 ± 0.074, 1.44 ± 0.163, 1.488 ± 0.221, 0.171 ± 0.049 respectively). However, the mean of levels of C-reactive and WBC protein was higher in DFU and DFU & CKD compared with normal control (P < 0.001). The best cutoff value, sensitivity, specificity, and area under the curve (AUC) for PCT's diagnostic accuracy in differentiating DFU were 0.231 ng/ml, 91.1%, 99.0%, and 0.946; P < 0.001 respectively. PCT increase in DFU groups Figure 1.

Correlation Between Procalcitonin and Cystatin C, CRP and WBC

The PCT values in DFU & CKD group were found positive significantly correlated with the levels of CRP (r = 0.882, P < 0.05), Similar picture was observed and found that in correlated with Cystatin C levels (r = 0.771, P < 0.05) and PCT levels had a significant positive correlation with WBC (r = 0.690, P < 0.01) and in DFU group were found PCT had positive correlation with CRP, Cystatin C, WBC (r = 0.480, 0.4, 0.761) (P < 0.05) respectively Table 3 and Figure 2.

Cystatin C and Kidney Injury Molecule-1 Parameters

The mean ± SD of serum Cystatin C and KIM-1. There was non-significant deference (P > 0.05) in mean of serum Cystatin C and KIM-1 found in patients' group (DM) compared with control group. Also there high significantly increased (P < 0.001) in mean serum cystatin C found in (DFU, DFU & CKD) groups when compared with control group. There was a high significant increase (P < 0.01) in mean serum KIM-1 found in (DFU group) and very high significant (P < 0.001) in DFU & CKD group when compared with the control group. As well as a high significant increase (P < 0.001) in mean serum KIM-1 found in (DFU, DFU & CKD) groups when compared with the DM group and a high significant increase (P < 0.001) between DFU group and DFU & CKD Table 4.

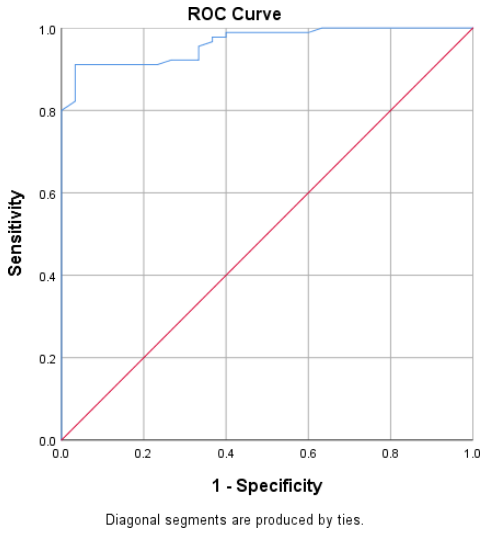

Fig. 1 **Receiver operating characteristic curve PCT showing sensitivity and specificity.**

Table 3. **Correlation analysis using person correlation of PCT in (DFU) and (DFU&CKD) groups**

Parameter PCT		CRP	Cystatin C	WBC
DFU group	R	0.480**	0.400*	0.761***
	P-value	0.007	0.02	0.0001
DFU & CKD group	R	0.882***	0.771***	0.690***
	P-value	0.0001	0.0001	0.0001

*Correlation significant at the 0.05 level (2-tailed,** Correlation significant at the 0.01 level (2-tailed),*** Correlation significant at the 0.001 level (2-tailed).

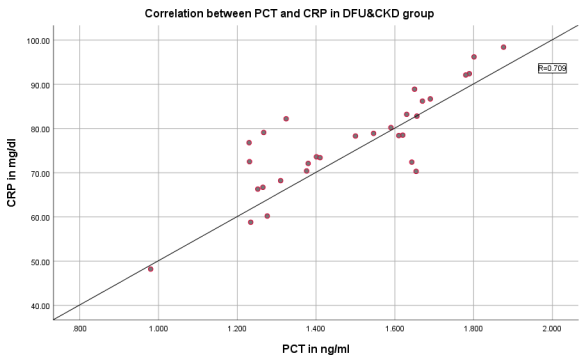

Fig. 2 **The correlation between serum levels of PCT (ng/ml) with CRP (mg/dl) in the Diabetic foot ulcer with chronic kidney disease group (*P* value = 0.001), (*R* = 0.709).**

Table 4. **The mean ± SD levels of Cystatin C and KIM-1 in all groups**

Parameters	Control mean ± SD n = 30	DM mean ± SD n = 30	DFU mean ± SD n = 30	DFU & CKD mean ± SD n = 30
Cystatin C ng/ml	0.53 ± 0.113	0.85 ± 0.16$^{a = ns}$	1.60 ± 0.59$^{a▲***\ b▲***}$	4.6 ± 0.61$^{a▲***\ b▲***\ c▲**}$
KIM-1 ng/ml	0.54 ± 0.04	0.76 ± 0.11$^{a = ns}$	1.28 ± 0.1$^{a▲**\ b▲***}$	5.4 ± 0.4$^{a▲***\ b▲***\ c▲**}$

N: Number, SD: Standard deviation, ▲, significant increase: *, ($P < 0.05$): **, ($P < 0.01$): ***, ($P < 0.001$): ns, non-significant: *a*, ANOVA test between control: DM, DFU and DFU & CKD groups: *b*, ANOVA test between DM and DFU, DFU & CKD groups, *c*, ANOVA test between DFU and DFU & CKD groups.

The ROC Analysis of PCT Parameters

The ROC analysis's findings demonstrate that PCT can distinguish and predict DFU patients from healthy individuals (AUC = 0.96). The sensitivity and specificity values were 99% and 93%, it was found the *P* value in terms of prior probability was 0.001, respectively, these shown in Figure 1.

Discussion

Our study demonstrates elevated levels of inflammatory markers such as PCT, as well as traditional markers like CRP and WBC, in patients with diabetic foot. The correlation between PCT and both CRP and WBC is a significant indicator of inflammation in diabetic foot disease, particularly in bacterial infections, whether localized or systemic.[14] Uzun et al. indicated that both PCT and WBC are essential for diagnosing diabetic foot ulcers (DFU).[8] The interest in the inflammatory basis of diabetes and its complications is supported by previous research highlighting the role of inflammation in the pathophysiology of diabetes mellitus (DM).[15] Numerous studies have shown that PCT has high specificity and sensitivity for diagnosing diabetic foot infections, supporting its use as a predictive marker in early infection, as PCT peaks within six hours.[16] Our study also found significantly higher levels of C-reactive protein (CRP) in individuals with diabetic foot compared to a healthy control group, indicating infection and inflammatory processes. This aligns with findings from Umapathy et al., who reported elevated CRP levels in diabetic foot infections, particularly in the infected DFU (IDFU) group compared to the non-infected DFU (NIDFU) group.[17] Similarly, the white blood cell (WBC) count was higher in our study's diabetic foot infection group, reflecting the severity of the infection causing diabetic foot ulcers. Higher WBC levels in diabetic foot disease are consistent with the findings of Ong et al., who observed increased WBC levels associated with a higher risk of major amputation in DFU patients.[18] Serum Cystatin C, another inflammatory marker linked to renal disease, was elevated in both the DFU and DFU with chronic kidney disease (CKD) groups compared to the non-DFU group. The association between elevated Procalcitonin and Cystatin C levels indicates a higher risk factor for diabetic foot ulcers. Ai L et al. found that increased Cystatin C was linked to higher long-term rates of community-acquired sepsis.[19] An et al. also reported that elevated Cystatin C significantly increased the rates of diabetic foot amputation compared to diabetic patients without kidney disease.[20] Additionally, Cystatin C is considered a sensitive biomarker for screening peripheral artery disease (PAD) in diabetic populations.[21] Our study found a significant relationship between Cystatin C and inflammation markers such as WBC and CRP. Kidney Injury Molecule-1 (KIM-1) is recognized as an indicator of kidney dysfunction in diabetic nephropathy patients.[13] Our results showed an increase in mean KIM-1 levels in both the diabetic foot group and the diabetic foot with CKD group. Diabetes mellitus induces oxidative stress in kidney tissue, significantly increasing serum levels and renal expression of KIM-1. KIM-1 is a phosphatidylserine receptor that recognizes apoptotic cells and directs them to lysosomes, transforming kidney proximal epithelial cells into semi-professional phagocytes.[22] De Silva et al. also found a significant increase in serum KIM-1 levels in chronic kidney disease patients.[23]

Conclusion

The present study shows that PCT levels are higher across all diabetic study groups and are associated with infection biomarkers (CRP and WBC), suggesting that PCT is a valuable diagnostic marker for early infection. Additionally, elevated levels of Cystatin C in DFU and DFU with CKD indicate that it is an important biomarker of kidney function and diabetes complications. The measurement of Cystatin C is crucial for identifying DM patients at higher risk of foot disease, making serum Cystatin C a useful early biomarker for diabetic foot in DM patients. The increase in mean KIM-1 levels in the diabetic foot group and the diabetic foot with CKD group indicates that KIM-1 is a pro-inflammatory marker elevated in diabetic foot and chronic kidney disease.

Conflict of Interest

None.

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